Chronic obstructive pulmonary disease and its comorbidities

Systemic consequences and associated comorbidities are highly prevalent in patients with chronic obstructive pulmonary disease and have a strong impact on morbidity and mortality. This review examines their prevalence and clinical features, and discusses the pathogenic mechanisms, prognosis and implications for therapy.

Chronic obstructive pulmonary disease is a condition that primarily affects the lungs and is characterized by poorly reversible airflow limitation, that is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases (Rodriguez-Roisin et al, 2009). Chronic obstructive pulmonary disease is complicated by the development of systemic consequences and comorbidities. Smoking is a risk factor for many of the systemic consequences of chronic obstructive pulmonary disease and comorbidities and is the most important risk factor for chronic obstructive pulmonary disease. Many of the systemic consequences of chronic obstructive pulmonary disease and comorbidities share systemic inflammation as a possible common mechanism (*Figure 1*).

Thus, chronic obstructive pulmonary disease can be associated with the presence of one or more distinct disorders that can be a direct or systemic consequence of chronic obstructive pulmonary disease or can be associated with co-existing conditions not necessarily related to chronic obstructive pulmonary disease (true comorbidities). Differentiating systemic consequences and comorbidities is not always easy and overlap between the two is common.

Recognized systemic consequences of chronic obstructive pulmonary disease and comorbidities include cardiovascular disease, diabetes, malnutrition involving loss of skeletal muscle mass and function, lung cancer, osteoporosis, infections, anaemia, increased gastro-oesophageal reflux, depression and anxiety (*Table 1*).

This review examines the prevalence and clinical features of the systemic consequences of chronic obstructive pulmonary disease and its associated comorbidities and describes their potential pathogenic mechanisms, their relevance for prognosis and implications for therapy.

Comorbidities associated with chronic obstructive pulmonary disease: are they important?

The prevalence of comorbidities associated with chronic obstructive pulmonary disease varies greatly between studies, but most reports suggest a high prevalence (Chatila et al, 2008) (*Table 2*). In one study only 6% of patients with chronic obstructive pulmonary disease did not have another chronic medical condition, with an average of 3.7 comorbidities in chronic obstructive pulmonary disease patients *vs* 1.8 in healthy controls (Mapel et al, 2000). Another study reported that over 50% of a cohort of 1522 patients with chronic obstructive pulmonary disease had one or two comorbidities, 15.8% had three or four comorbidities and 6.8% had five or more (van Manen et al, 2001).

Not only are comorbidities highly prevalent, but they also have important prognostic implications. Although chronic obstructive pulmonary disease is a

Figure 1. Systemic consequences and comorbidities related to chronic obstructive pulmonary disease. Cigarette smoking triggers local (lung) and systemic inflammation, which has been related to a variety of systemic consequences and comorbidities occurring in patients with chronic obstructive pulmonary disease. IHD = ischaemic heart disease.

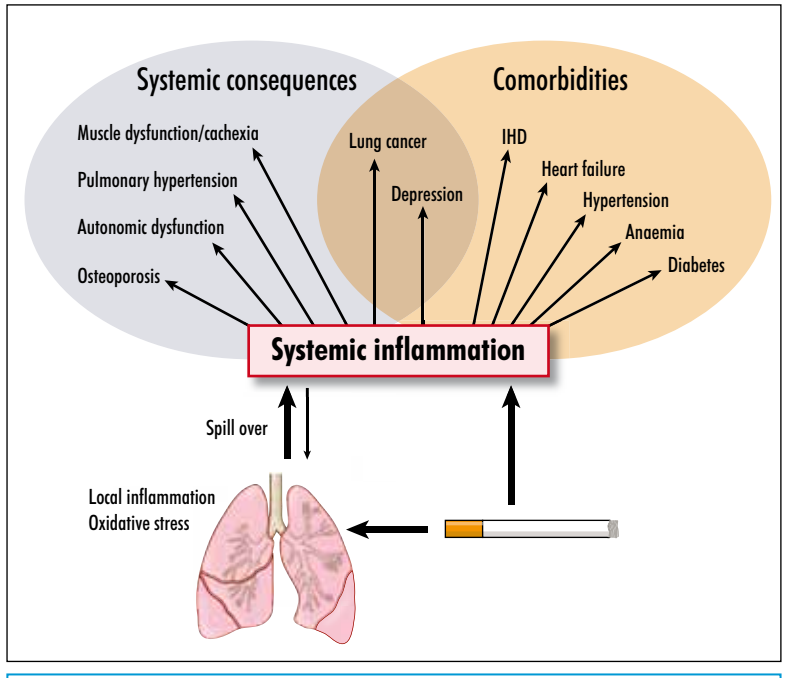

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Table 1. Most common systemic consequences and comorbidities in chronic obstructive pulmonary disease

Cardiovascular disease (e.g. coronary artery disease, heart failure, pulmonary hypertension)
Diabetes
Loss of skeletal muscle mass and function
Lung cancer
Osteoporosis
Infections
Anaemia
Gastro-oesophageal reflux
Depression and anxiety

progressive disease leading to respiratory failure in the end stages of the disease, chronic obstructive pulmonary disease is not always the primary cause of death in this population; these patients die more frequently of other conditions. In the Lung Health Study of patients with mild to moderate chronic obstructive pulmonary disease, deaths caused by respiratory disease were relatively uncommon – 7.8%, excluding lung cancer, which was the most common cause of death (33%). Coronary heart disease accounted for 10.5%, and cardiovascular disease including coronary heart disease accounted for 22% of deaths. Cancer of organs other than the lung accounted for 21% of deaths (Anthonisen et al, 2005).

In the Towards a Revolution in COPD Health (TORCH) study (McGarvey et al, 2007), of inhaled corticosteroids and/or long-acting beta agonists in patients with moderate to severe chronic obstructive pulmonary disease, the cause of death, as assessed by an independent review panel, was attributed to chronic obstructive pulmonary disease in 27%, cardiovascular causes in 26%, other respiratory causes 9% and cancer in 21%, with 10% having other causes and 8% of unknown cause. Mannino and co-workers (2008) reported, in a cohort of 10 009 patients with chronic obstructive pulmonary disease, that the presence of diabetes, hypertension or cardiovascular disease significantly increased the risk of hospitalization or mortality. As the disease progresses, the incidence of comorbidities increases, and combinations of multiple comorbid diseases in an individual result in an even higher risk of death (*Figure 2*). In a cohort of 45 000 chronic obstructive pulmonary disease patients, heart failure was the leading cause of hospitalization, followed by myocardial infarction and stroke (Sidney et al, 2005). The presence of other medical conditions has been reported to increase the duration of hospitalizations for patients with chronic obstructive pulmonary disease by 36.5% (Kinnunen et al, 2003).

Chronic obstructive pulmonary disease is a complex disease involving more than airflow limitation. Comorbidities and systemic manifestations have a prognostic implication. The addition of other domains of the disease besides lung function (body composition, exercise tolerance and dyspnoea) increases the ability to predict several outcomes, explaining why a multidimensional grading system such as the BODE index is a better predictor of mortality than forced expiratory volume in 1 second alone (Celli et al, 2004).

Pathogenic mechanisms

Cigarette smoking is the most important established risk factor for chronic obstructive pulmonary disease and is a major risk factor for many of its systemic consequences and comorbidities. Heart failure, arrhythmias, hypertension, peripheral and coronary artery diseases, diabetes, osteoporosis, cancer, pulmonary vascular abnormalities, psychiatric disorders, muscle dysfunction or wasting, and infections are the most common systemic consequences of chronic obstructive pulmonary disease and comorbidities that are related to smoking (Chatila et al, 2008).

Cigarette smoking has also been associated with insulin resistance, systemic oxidative stress and inflammation, factors which have also been associated with endothelial dysfunction and cardiovascular disease (Yanbaeva et al, 2007). A meta-analysis has shown that a proportion of clinically stable patients with chronic obstructive pulmonary disease have evidence of systemic inflammation (Gan et al, 2004).

Table 2. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease

Reference	*n*	Arthritis	Cardiac	Hypertension	Diabetes	Lipids	Psychological disorders	Gastrointestinal disturbances	Cancer	Osteoporosis
van Manen et al (2001)	1145	36	13	23	5	NA	9	15	6	NA
Mapel et al (2000)	200	22	65	45	12	NA	17	32	18	NA
Soriano et al (2005)	2699	28	22	NA	NA	NA	10	26	4	NA
Sidney et al (2005)	45 966	NA	18	18	2	9	NA	NA	NA	NA
Walsh and Thomashow (2006)	3000	70	50	52	16	51	38	62	4	32

NA = data not available. From Chatila et al (2008)

Systemic inflammation, either as increased circulating cytokines, chemokines and acute phase proteins, or as abnormalities in circulating cells, has been demonstrated in patients with chronic obstructive pulmonary disease, particularly when the disease is severe or during exacerbations (Agusti et al, 2003; Gan et al, 2004). Systemic inflammation in chronic obstructive pulmonary disease is associated with an accelerated decline in lung function (Donaldson et al, 2005). Elevated levels of circulating C-reactive protein, a marker of systemic inflammation, have been associated with reduced exercise tolerance and health-related quality of life (Broekhuizen et al, 2006) and with increased risk of hospitalizations and mortality (Dahl et al, 2007).

Several mechanisms have been proposed for the systemic inflammation that occurs in patients with chronic obstructive pulmonary disease. These include the effects of smoking, 'spill over' of inflammatory mediators from lung inflammation, skeletal muscle as a source of systemic inflammation, hyperinflation of the lungs, stimulation of the bone marrow, and the effect of tissue hypoxia.

There is direct evidence that protein moves from the lung to lymph and blood. Experimental data indicate that alveolar macrophages and bronchial epithelial cells are critically important in processing inhaled noxious gases and particles, and that the mediators they produce are also identified in the systemic response in chronic obstructive pulmonary disease (Sinden and Stockley, 2010). Moreover, systemic inflammation is a recognized risk factor for a number of conditions that are associated with chronic obstructive pulmonary disease.

Lung function declines with age. An accelerated rate of lung function decline is a key defining feature of chronic obstructive pulmonary disease (Celli and MacNee, 2004). Ageing itself is associated with chronic degenerative disorders and when compared to healthy controls, telomere length, a marker of cellular ageing, is reduced in smokers with normal lung function (Morla et al, 2006) and reduced further in chronic obstructive pulmonary disease patients (Savale et al, 2009), particularly in patients with emphysema (Tsuji et al, 2006). Telomere length has also been correlated with arterial wall stiffness which reflects ageing of the vasculature (Benetos et al, 2001). These data suggest that the destruction of the lung parenchyma, leading to emphysema, and the increased cardiovascular risk may share mechanisms related to accelerated ageing.

Thus, chronic obstructive pulmonary disease and some of its systemic consequences and comorbidities share the same risk factors. On the other hand, chronic obstructive pulmonary disease may trigger inflammation, inducing a cause–effect relationship between chronic obstructive pulmonary disease and some of its systemic manifestations. For example, chronic obstructive pulmonary disease is an independent risk factor for cardiovascular disease. For every 10% decrease in forced expiratory volume in 1 second, cardiovascular mortality increases by approximately 28% and non-fatal coronary events increase by approximately 20% in mild to moderate chronic obstructive pulmonary disease (Anthonisen et al, 2002). Indeed, chronic obstructive pulmonary disease is associated with increased systemic arterial stiffness (Mills et al, 2008), which is a marker of increased cardiovascular risk, and is independently associated with emphysema as assessed by computed tomography scanning (McAllister et al, 2007), suggesting that the mechanisms resulting in lung tissue damage may also be related to systemic abnormalities leading to increased cardiovascular risk.

Whatever the mechanisms leading to systemic consequences of chronic obstructive pulmonary disease and comorbidities, their presence worsens the prognosis of these patients.

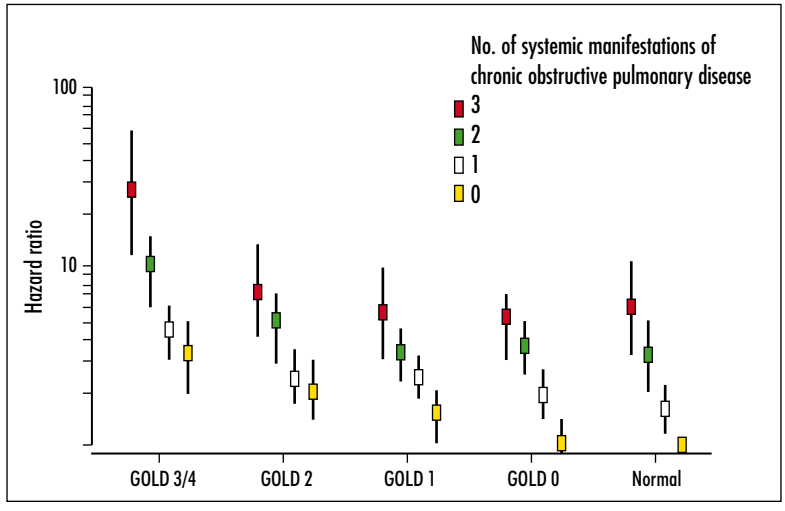

Figure 2. Prevalence and outcomes of the presence of zero to three comorbidities (diabetes, hypertension and cardiovascular disease) in chronic obstructive pulmonary disease: results from Cox proportional hazard models (presented as hazard ratio with 95% confidence interval) prediction of time to first hospitalization within 5 years. The reference group (normal) was subjects with normal lung function for each comorbid disease. Models were adjusted for age, sex, race, smoking status, education level and body mass index. Modified with permission from Mannino et al (2008). GOLD = Global initiative for chronic Obstructive Lung Disease.

Clinical features

Osteoporosis

Several studies have reported an increased prevalence of osteoporosis and low bone mineral density in patients with chronic obstructive pulmonary disease. In the TORCH study, 18% of men and 30% of women had osteoporosis, while 42% of men and 41% of women had osteopenia based on bone mineral density assessments (Ferguson et al, 2009). Several risk factors for osteoporosis are common features in chronic obstructive pulmonary disease patients, namely ageing, limited physical activity, vitamin D deficiency, cigarette smoking, hypogonadism and the use of systemic corticosteroids. A meta-analysis (van Staa et al, 2002) concluded that more

than 6.25 mg prednisolone daily led to decreased bone mineral density and increased fracture risk. The effect of inhaled corticosteroids is debatable. Indeed, chronic obstructive pulmonary disease is associated with osteoporosis independent of the use of systemic corticosteroids (Iqbal et al, 1999). As a consequence of osteoporosis, the prevalence of vertebral fractures in patients with chronic obstructive pulmonary disease is 20–30%. This can result in increased kyphosis which may adversely affect pulmonary function.

Osteoporosis is related to emphysema (Ohara et al, 2008) and to arterial wall stiffness (Sabit et al, 2007). The osteoprotegerin/receptor activator of nuclear factor-kB (RANK)/RANK ligand system has been identified as a possible mediator of arterial calcification, suggesting common links between osteoporosis and vascular disease (D'Amelio et al, 2009).

Skeletal muscle dysfunction or wasting

Peripheral muscle dysfunction is a prominent contributor to exercise limitation (Saey et al, 2003) and increased health-care utilization, and is an independent predictor of morbidity and mortality in patients with chronic obstructive pulmonary disease (Agusti et al, 2003). Peripheral muscle strength, endurance and fatiguability are impaired in chronic obstructive pulmonary disease. Muscle dysfunction is characterized by two related phenomena: malfunctioning of the muscle and net loss of muscle mass. Muscle mass loss is present in 18–36% of patients with chronic obstructive pulmonary disease and is responsible for weight loss evident in 17–35% of chronic obstructive pulmonary disease patients depending on the population studied (Schols et al, 1993). Indeed, muscle wasting is present in 6–21% of patients with normal weight (Schols et al, 1993). Moreover, muscle loss relates to muscle strength and exercise (in)tolerance independent of the degree of airway obstruction (Schols et al, 1991). Factors relevant to skeletal muscle dysfunction include:

1. Balance between protein synthesis and breakdown
2. Nutritional abnormalities
3. Muscle disuse
4. Systemic corticosteroids
5. Tissue hypoxia and hypercapnia
6. Alterations in muscle remodelling
7. Inflammation
8. Oxidative or nitrosative stress
9. Mitochondrial abnormalities (Rabinovich and Vilaro, 2010).

Cardiovascular disease

Coronary artery disease is very prevalent in chronic obstructive pulmonary disease patients (Sin et al, 2005b). Chronic obstructive pulmonary disease shares common risk factors with coronary artery disease such as cigarette smoking, sedentarism and older age. Systemic arterial stiffness, a good predictor of vascular disease, is increased in chronic obstructive pulmonary disease patients compared to non-smokers and smokers with normal lung function, even after correction for smoking history (Maclay et al, 2009). In fact, arterial wall stiffness is associated with emphysema independent of other factors such as smoking history, suggesting that chronic obstructive pulmonary disease is an independent risk for coronary artery disease (Sin and Man, 2005; McAllister et al, 2007). The same is true for airflow limitation, since the forced expiratory volume in 1 second is an independent predictor of death from myocardial infarction (Anthonisen et al, 2005). The risk of death from myocardial infarction in chronic obstructive pulmonary disease patients is independent of age, sex and smoking history (Sin et al, 2005b). Systemic inflammation has also been implicated in the pathogenesis of atherosclerotic plaques. This pathogenic mechanism is shared with chronic obstructive pulmonary disease.

The association of chronic obstructive pulmonary disease with left ventricular dysfunction is less well documented, but Rutten et al (2006) showed 20% of chronic obstructive pulmonary disease patients had left ventricular dysfunction.

Pulmonary arterial hypertension is another cardiovascular manifestation in patients with chronic obstructive pulmonary disease. Approximately 50% of severe and very severe chronic obstructive pulmonary disease patients have pulmonary arterial hypertension (Thabut et al, 2005). Mild patients do not commonly have pulmonary arterial hypertension at rest but may develop it during exercise. From 1–3% of chronic obstructive pulmonary disease patients have pulmonary arterial hypertension disproportionate to the degree of airway obstruction which behaves like primary pulmonary arterial hypertension (Barbera et al, 2003). Hypoxic vasoconstriction, endothelial injury by cigarette smoke and inflammation are potential pathogenic mechanisms for the development of pulmonary arterial hypertension in chronic obstructive pulmonary disease patients (Giaid and Saleh, 1995; Peinado et al, 1999).

Anaemia

Although sustained hypoxaemia can be associated with secondary erythrocytosis as a compensatory mechanism to improve oxygen transport to the tissues, polycythaemia is only present in approximately 6% of chronic obstructive pulmonary disease patients, while anaemia is a more common finding (13–33%; Similowski et al, 2006). The anaemia in chronic obstructive pulmonary disease is normochromic normocytic and is likely to be mediated by shortened red blood cell survival, erythropoietin resistance and dysregulation of iron homeostasis (Weiss and Goodnough, 2005).

Anaemia contributes to impaired oxygen transport to the tissues and exercise intolerance and has been reported to be associated with increased mortality (Similowski et al, 2006).

Infections

Owing to the normal lung's defence mechanisms, lower respiratory infections in the absence of lung disease are relatively infrequent. Both acute and chronic lower respiratory tract infections occur with increased frequency in chronic obstructive pulmonary disease patients. The frequency of respiratory infections is also likely to be more significant in the airway (chronic bronchitis) than in the parenchymal (emphysema) phenotype of chronic obstructive pulmonary disease.

Infection in chronic obstructive pulmonary disease may be partly related to smoking, but worsens when airflow obstruction develops in smokers (Sethi, 2010). Recurrent viral and bacterial infections are clearly linked to exacerbations of the disease. Also important is the recognition of a chronic infection cycle whereby, once the innate lung defence is impaired by tobacco smoking, microbial colonization results in chronic inflammation and lung destruction. A major cause of hospitalization and death is community-acquired pneumonia, most commonly seen in smokers and patients with chronic obstructive pulmonary disease (Ginesu and Pirina, 1995).

Depression

Depression has been reported in up to 42% of patients with chronic obstructive pulmonary disease, being 2–5% higher than in the normal age-matched population (Hill et al, 2008).

Depression in chronic obstructive pulmonary disease is part of a vicious cycle involving poor health status leading to depression leading to isolation leading to sedentarism leading to worsening of health status. The latter could constitute a mechanism for the development of reactive depression: chronic obstructive pulmonary disease leading to poor health status leading to depression. On the other hand, depression may precede the development of chronic obstructive pulmonary disease. In this respect, cigarette smoking is more frequent in subjects with anxiety and depression. There is increasing evidence that systemic inflammation could also contribute to the development of symptoms of depression (Anisman et al, 2008).

Lung cancer

Lung cancer is three to four times more frequent in chronic obstructive pulmonary disease patients than in the general population and is an important cause of mortality (causes 7–38% of chronic obstructive pulmonary disease mortality) (Wasswa-Kintu et al, 2005).

Patients with chronic obstructive pulmonary disease have a higher incidence of lung cancer independent of the history of smoking (Wasswa-Kintu et al, 2005). Indeed, smoking cessation does not appear to reduce the risk of lung cancer in these patients (Anthonisen et al, 2005). Even a small reduction in lung function in smokers is associated with a significant increase in the risk of lung cancer (Wasswa-Kintu et al, 2005). Chronic obstructive pulmonary disease is associated with the risk of developing small cell and squamous cell carcinoma (Wasswa-Kintu et al, 2005) while it seems that there is no relationship between chronic obstructive pulmonary disease and the risk of developing adenocarcinoma (Malhotra et al, 2006). The risk of developing lung cancer is also higher in female chronic obstructive pulmonary disease patients than in males (Ben-Zaken et al, 2007). Observational studies revealed an association between mortality and the presence of emphysema and chronic bronchitis, even in non-smokers (Turner et al, 2007). Indeed, mortality as a result of lung cancer seems to be higher in patients with chronic obstructive pulmonary disease than in patients without the disease (Kiri et al, 2010). Whether this is related to a poor health status, inflammatory factors or others remains to be seen.

Diabetes

Population studies have shown a prevalence of 1–16% of diabetes among the chronic obstructive pulmonary disease population (Mannino et al, 2008). Smoking is also a risk factor and quitting reduces the risk of diabetes (Manson et al, 2000). A reduction in lung function has also been associated with diabetes (Engstrom and Janzon, 2002). Inflammatory markers such as tumour necrosis factor-alpha, interleukin-6 and C-reactive protein have been associated with diabetes; they are elevated in chronic obstructive pulmonary disease and may mediate insulin resistance by blocking signalling through the insulin receptor. The metabolic syndrome also appears more common among chronic obstructive pulmonary disease patients, reflecting the concurrence of diabetes and cardiovascular disease with airways obstruction (Poulain et al, 2008).

Gastro-oesophageal reflux

An increased incidence of gastro-oesophageal reflux disease has been seen in the chronic obstructive pulmonary disease population, being more common in patients with a forced expiratory volume in 1 second below 50% predicted (Mokhlesi et al, 2001). Gastro-oesophageal reflux disease also appears to be a precipitant of exacerbations of chronic obstructive pulmonary disease (Rogha et al, 2010). However, the nature and significance of this association remains unknown.

Implications for management

The implications of systemic consequences of chronic obstructive pulmonary disease and comorbidities on prognosis in chronic obstructive pulmonary disease patients highlight the need for active identification and treatment. Careful cardiovascular, metabolic and endocrine history and examination should be performed when assessing patients with chronic obstructive pulmonary disease.

Pulmonary rehabilitation should be considered for all patients in whom respiratory symptoms are associated with diminished functional capacity or reduced health-related quality of life (Nici et al, 2006). Chronic obstructive pulmonary disease patients at all stages of disease benefit from exercise training programmes, improving with respect to both exercise tolerance and symptoms of dyspnoea and fatigue (Rodriguez-Roisin et al, 2009). Attempts should be made to identify patients with anaemia. Bone mineral density should be measured, either by dual-emission X-ray absorptiometry or computed tomography in all patients with Global initiative for chronic Obstructive Lung Disease (GOLD) grade III and IV, particularly in patients with low fat free mass.

Treating systemic consequences of chronic obstructive pulmonary disease and comorbidities

Dietary supplementation with calcium and vitamin D as well as enrolment in pulmonary rehabilitation programmes are helpful in treating osteoporosis. Patients with osteoporosis should be treated with a bisphosphonate (Smith et al, 2004; Ebeling, 2008). Minimizing deconditioning, enrolling in pulmonary rehabilitation and avoiding systemic corticosteroids should be measures implemented to tackle skeletal muscle dysfunction or wasting.

So far the results of nutritional supplementation and hormonal replacement in patients with low body mass index have not been encouraging (Burdet et al, 1997; Creutzberg et al, 2000). However, individual subjects may benefit from nutritional supplementation with a reduction in mortality (Schols, 1998). Exercise training is the most successful strategy to treat muscle dysfunction or wasting in patients with chronic obstructive pulmonary disease: it improves exercise tolerance through improving muscle strength, endurance and reducing fatigue (Nici et al, 2006). Exercise training improves body weight through improving fat free mass, skeletal muscle oxidative capacity and fibre type distribution and is clearly recommended for chronic obstructive pulmonary disease patients with exercise intolerance independent of the degree of severity of airway obstruction (Nici et al, 2006).

Efforts should be made to identify and control risk factors for cardiovascular disease such as dyslipidaemia, hypertension, diabetes and sedentarism. Treatment of anaemia with erythropoietin is unlikely to be useful as there is end-organ resistance and blood transfusions might be indicated. Iron supplements are likely to be detrimental as iron cannot be used correctly and may increase systemic oxidative stress.

Current guidelines recommend the use of antibiotics for moderate and severe exacerbations. Ongoing studies are examining intermittent treatment with inhaled and oral fluoroquinolones and chronic treatment with low-dose macrolides in patients with chronic obstructive pulmonary disease and repeated exacerbations. Results of these studies will determine whether such treatment is effective and safe (Sethi, 2010).

Depression often remains untreated in patients with chronic obstructive pulmonary disease. There is a need for large, well-controlled trials assessing the effectiveness of antidepressants in the treatment of depression in chronic obstructive pulmonary disease. Pulmonary rehabilitation alone improves anxiety and depression (Paz-Diaz et al, 2007). Psychotherapy added to pulmonary rehabilitation can significantly reduce depression in chronic obstructive pulmonary disease (de Godoy and de Godoy, 2003).

Efforts should be made in the control of diabetes associated with chronic obstructive pulmonary disease.

Early identification of malignancy may allow better treatment in chronic obstructive pulmonary disease patients.

Targeting inflammation

Systemic inflammation, whether or not it originates in the lungs, may be a common link to many of the systemic consequences of chronic obstructive pulmonary disease and comorbidities, so is a potential target to prevent the development and evolution of the systemic manifestations of chronic obstructive pulmonary disease, although this strategy remains unproven. Several studies have evaluated the effects of modifying inflammation using some of the well-established treatments for chronic obstructive pulmonary disease. Other studies have explored the effect of drugs that are not normally used for the treatment of chronic obstructive pulmonary disease patients.

Cigarette smoking is a common link between chronic obstructive pulmonary disease and the systemic consequences of chronic obstructive pulmonary disease and its comorbidities. Smoking cessation programmes should be considered for patients who continue to smoke. This may reduce systemic inflammation and its associated risks.

The effects of inhaled corticosteroids on prognosis and inflammation in chronic obstructive pulmonary disease are controversial. A meta-analysis showed a reduction in all causes of mortality, including cardiovascular mortality (Sin et al, 2005a). However, large clinical trials found a non-significant reduction in all-cause mortality (Calverley et al, 2007). Inhaled corticosteroids have not been shown to reduce markers of systemic inflammation such as C-reactive protein (Sin et al, 2008).

Other drugs not regularly used in the treatment of chronic obstructive pulmonary disease can be used to treat systemic consequences or comorbidities and may thus be of benefit to these patients. Pharmaco-epidemiological studies have suggested that statins and angiotensin-converting enzyme inhibitors, used in the treatment of comorbid diseases, may have a benefit in chronic obstructive pulmonary disease patients because of their anti-inflammatory effects (Mancini et al,

2006). As well as reducing cholesterol levels, statins also have anti-inflammatory, antioxidant and immunomodulatory effects which may act on other systemic consequences of chronic obstructive pulmonary disease and comorbidities.

Angiotensin-converting enzyme inhibitors are used to treat hypertension, heart failure and diabetes, all of which are comorbidities. Moreover, angiotensin-converting enzyme gene polymorphisms are associated with impaired muscle strength in patients with chronic obstructive pulmonary disease (Hopkinson et al, 2004).

A pharmaco-epidemiological study (Mancini et al, 2006) suggested that statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and the combination of statins with either of the other medications reduced hospitalization, myocardial infarction and death in patients with chronic obstructive pulmonary disease.

Other potential pharmacological treatments

Peroxisome-proliferator-activated receptors (PPARs) and PPAR-γ co-activator 1α are key regulators of skeletal muscle oxidative capacity, mitochondrial biogenesis and fibre-type shift towards more oxidative fibres. Reduced PPARδ protein levels and PPAR-γ co-activator 1α mRNA expression are present in the skeletal muscle of patients with chronic obstructive pulmonary disease (Remels et al, 2007), particularly in cachectic patients. So far, no trials with PPAR agonists have been reported in chronic obstructive pulmonary disease.

Phosphodiesterase-4 inhibitors such as roflumilast are effective in inhibiting airway inflammation (Grootendorst et al, 2007) but not systemic inflammation. Their effects on systemic consequences of chronic obstructive pulmonary disease and comorbidities are unknown.

Owing to their implied role in the pathogenesis of several of the systemic consequences of chronic obstructive pulmonary disease and comorbidities, there is a case for potential treatment with drugs targeting oxidative stress, NFkB and P38 mitogen-activated protein kinase. Several molecules are under development or in clinical trials in chronic obstructive pulmonary disease.

Conclusions

The high prevalence of systemic consequences and comorbidities associated with chronic obstructive pulmonary disease highlights the fact that chronic obstructive pulmonary disease goes beyond the lungs and is associated with extra-pulmonary manifestations that have an impact on morbidity and mortality. Different phenotypes of the disease can be defined and identifying the systemic consequences and comorbidities associated with chronic obstructive pulmonary disease allows for better characterization and management of the patients. Indeed, multidimensional grading systems that take into account not only lung function, but also parameters reflecting the patient's perception and the systemic impact of the disease, show a greater ability to predict important outcomes such as mortality, than lung function assessment alone (Celli et al, 2004). Efforts should be made to identify the systemic consequences and comorbidities associated with the disease to improve the management of individual patients. It is reasonable to hope that more comprehensive management of chronic obstructive pulmonary disease, that takes into account its systemic consequences and comorbidities, may improve the assessment of the severity and improve the response to treatment, reducing mortality in patients with chronic obstructive pulmonary disease.

Future studies with PDE4, NFkB, P38 mitogen-activated protein kinase or new antioxidants may reveal the usefulness of this therapy. Prospective trials of statins, angiotensin-converting enzyme inhibitors, PPAR agonists and beta blockers are needed to establish the potential relevance of these drugs in the management of chronic obstructive pulmonary disease patients. **BJHM**

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Conflict of interest: none.

Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X (2003) Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J* **21**(2): 347–60

Anisman H, Merali Z, Hayley S (2008) Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: comorbidity between depression and neurodegenerative disorders. *Prog Neurobiol* **85**(1): 1–74

Anthonisen NR, Connett JE, Enright PL, Manfreda J (2002) Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* **166**(3): 333–9

Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE (2005) The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* **142**(4): 233–9

Barbera JA, Peinado VI, Santos S (2003) Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* **21**(5): 892–905

Ben-Zaken CS, Pare PD, Man SF, Sin DD (2007) The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke

KEY POINTS

- Chronic obstructive pulmonary disease is a complex disease involving more than just the lungs.
- The disease is complicated by the development of comorbidities and systemic consequences.
- The most frequent systemic consequences and comorbidities are cardiovascular disease, diabetes, skeletal muscle dysfunction, lung cancer, osteoporosis, infections, anaemia, gastro-oesophageal reflux and depression or anxiety.
- Comorbidities and systemic consequences share some pathogenic mechanisms such as inflammation and cigarette smoking.
- Systemic consequences and comorbidities have a prognostic implication in patients with chronic obstructive pulmonary disease.
- Management of patients with chronic obstructive pulmonary disease may include the active identification and treatment of comorbidities and systemic consequences.

metabolism. *Am J Respir Crit Care Med* **176**(2): 113–20
Benetos A, Okuda K, Lajemi M et al (2001) Telomere length as an indicator of biological aging: The gender effect and relation with pulse pressure and pulse wave velocity. *Hypertension* **37**(2): 381–5
Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM (2006) Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax* **61**(1): 17–22
Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW (1997) Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med* **156**(6): 1800–6
Calverley PM, Anderson JA, Celli B et al (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* **356**(8): 775–89
Celli BR, Cote CG, Marin JM et al (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* **350**(10): 1005–12
Celli BR, MacNee W (2004) Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* **23**(6): 932–46
Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ (2008) Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* **5**(4): 549–55
Creutzberg EC, Schols AMWJ, Weling-Scheepers CAPM, Buurman WAW, Wouters EF (2000) Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **161:** 745–52
D'Amelio P, Isaia G, Isaia GC (2009) The osteoprotegerin/RANK/RANKL system: a bone key to vascular disease. *J Endocrinol Invest* **32**(4 Suppl): 6–9
Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG (2007) C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **175**(3): 250–5
de Godoy DV, de Godoy RF (2003) A randomized controlled trial of the effect of psychotherapy on anxiety and depression in chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* **84**(8): 1154–7
Donaldson GC, Seemungal TA, Patel IS et al (2005) Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* **128**(4): 1995–2004
Ebeling PR (2008) Clinical practice. Osteoporosis in men. *N Engl J Med* **358**(14): 1474–82
Engstrom G, Janzon L (2002) Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* **19**(2): 167–70
Ferguson GT, Calverley PM, Anderson JA et al (2009) Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. *Chest* **136**(6): 1456–65
Gan WQ, Man SF, Senthilselvan A, Sin DD (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* **59**(7): 574–80
Giaid A, Saleh D (1995) Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* **333**(4): 214–21
Ginesu F, Pirina P (1995) Etiology and risk factors of adult pneumonia. *J Chemother* **7**(4): 277–85
Grootendorst DC, Gauw SA, Verhoosel RM et al (2007) Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* **62**(12): 1081–7
Hill K, Geist R, Goldstein RS, Lacasse Y (2008) Anxiety and depression in end-stage COPD. *Eur Respir J* **31**(3): 667–77
Hopkinson NS, Nickol AH, Payne J et al (2004) Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **170**(4): 395–9
Iqbal F, Michaelson J, Thaler L, Rubin J, Roman J, Nanes MS (1999) Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. *Chest* **116**(6): 1616–24
Kinnunen T, Saynajakangas O, Tuuponen T, Keistinen T (2003) Impact of comorbidities on the duration of COPD patients' hospital episodes. *Respir Med* **97**(2): 143–6
Kiri VA, Soriano J, Visick G, Fabbri L (2010) Recent trends in lung cancer and its association with COPD: an analysis using the UK GP Research Database. *Prim Care Respir J* **19**(1): 57–61
Maclay JD, McAllister DA, Mills NL et al (2009) Vascular dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 180(6): 513–20
Malhotra S, Lam S, Man SF, Gan WQ, Sin DD (2006) The relationship between stage 1 and 2 non-small cell lung cancer and lung function in men and women. *BMC Pulm Med* **6:** 2
Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM (2006) Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* **47**(12): 2554–60
Mannino DM, Thorn D, Swensen A, Holguin F (2008) Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* **32**(4): 962–9
Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH (2000) A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* **109**(7): 538–42
Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB (2000) Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. *Arch Intern Med* **160**(17): 2653–8
McAllister DA, Maclay JD, Mills NL et al (2007) Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **176**(12): 1208–14
McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA (2007) Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* **62**(5): 411–15
Mills NL, Miller JJ, Anand A et al (2008) Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax* **63**(4): 306–11
Mokhlesi B, Morris AL, Huang CF, Curcio AJ, Barrett TA, Kamp DW (2001) Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. *Chest* **119**(4): 1043–8
Morla M, Busquets X, Pons J, Sauleda J, MacNee W, Agusti AG (2006) Telomere shortening in smokers with and without COPD. *Eur Respir J* **27**(3): 525–8
Nici L, Donner C, Wouters E et al (2006) American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* **173**(12): 1390–413
Ohara T, Hirai T, Muro S et al (2008) Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. *Chest* **134**(6): 1244–9
Paz-Diaz H, Montes de OM, Lopez JM, Celli BR (2007) Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. *Am J Phys Med Rehabil* **86**(1): 30–6
Peinado VI, Barbera JA, Abate P, Ramirez J, Roca J, Santos S, Rodriguez-Roisin R (1999) Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **159**(5 Pt 1): 1605–11
Poulain M, Doucet M, Drapeau V, Fournier G, Tremblay A, Poirier P, Maltais F (2008) Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. *Chron Respir Dis* **5**(1): 35–41
Rabinovich RA, Vilaro J (2010) Structural and functional changes of peripheral muscles in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* **16**(2): 123–33
Remels AH, Schrauwen P, Broekhuizen R, Willems J, Kersten S, Gosker HR, Schols AM (2007) Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur Respir J* **30**(2): 245–52
Rodriguez-Roisin R, Anzueto A, Bourbeau J, Calverley P (2009) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=989 (accessed 23 February 2011)
Rogha M, Behravesh B, Pourmoghaddas Z (2010) Association of gastroesophageal reflux disease symptoms with exacerbations of chronic obstructive pulmonary disease. *J Gastrointestin Liver Dis* **19**(3): 253–6
Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes, AW (2006) Heart failure and chronic obstructive pulmonary disease: An ignored combination? *Eur J Heart Fail* **8**(7): 706–11
Sabit R, Bolton CE, Edwards PH et al (2007) Arterial stiffness and

osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **175**(12): 1259–65
Saey D, Debigare R, Leblanc P, Mador MJ, Cote CH, Jobin J, Maltais F (2003) Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **168**(4): 425–30
Savale L, Chaouat A, Bastuji-Garin S et al (2009) Shortened telomeres in circulating leukocytes of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **179**(7): 566–71
Schols AMWJ (1998) Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **157:** 1791–7
Schols AM, Mostert R, Soeters PB, Wouters EF (1991) Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax* **46**(10): 695–9
Schols AMWJ, Soeters PB, Dingemans AMC, Mostert R, Frantzen PJ, Wouters EFM (1993) Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* **147:** 1151–6
Sethi S (2010) Infection as a comorbidity of COPD. *Eur Respir J* **35**(6): 1209–15
Sidney S, Sorel M, Quesenberry CP Jr DeLuise C, Lanes S, Eisner MD (2005) COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* **128**(4): 2068–75
Similowski T, Agusti A, MacNee W, Schonhofer B (2006) The potential impact of anaemia of chronic disease in COPD. *Eur Respir J* **27**(2): 390–6
Sin DD, Man SF (2005) Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* **21:** 8–11
Sin DD, Wu L, Anderson JA et al (2005a) Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* **60**(12): 992–7
Sin DD, Wu L, Man SF (2005b) The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* **127**(6): 1952–9
Sin DD, Man SF, Marciniuk DD et al (2008) The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **177**(11): 1207–14
Sinden NJ, Stockley RA (2010) Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. *Thorax* **65**(10): 930–6
Smith BJ, Laslett LL, Pile KD et al (2004) Randomized controlled trial of alendronate in airways disease and low bone mineral density. *Chron Respir Dis* **1**(3): 131–7
Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL (2005) Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* **128**(4): 2099–107
Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, Mal H (2005) Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* **127**(5): 1531–6
Tsuji T, Aoshiba K, Nagai A (2006) Alveolar cell senescence in patients with pulmonary emphysema. *Am J Respir Crit Care Med* **174**(8): 886–93
Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ (2007) Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* **176**(3): 285–90.
van Manen JG, Bindels PJ, Ijzermans CJ, van der Zee JS, Bottema BJ, Schadé E (2001) Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* **54**(3): 287–93
van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* **13**(10): 777–87
Walsh JW, Thomashow BM (2006) COPD and comorbidities: result of COPD Foundation national survey. Paper presented at American Thoracic Society International Conference, San Diego, California: 19–24 May
Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD (2005) Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* **60**(7): 570–5
Weiss G, Goodnough LT (2005) Anemia of chronic disease. *N Engl J Med* **352**(10): 1011–23
Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF (2007) Systemic effects of smoking. *Chest* **131**(5): 1557–66