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Comorbidities of COPD

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ABSTRACT By 2020, chronic obstructive pulmonary disease (COPD) will be the third cause of mortality. Extrapulmonary comorbidities influence the prognosis of patients with COPD. Tobacco smoking is a common risk factor for many comorbidities, including coronary heart disease, heart failure and lung cancer. Comorbidities such as pulmonary artery disease and malnutrition are directly caused by COPD, whereas others, such as systemic venous thromboembolism, anxiety, depression, osteoporosis, obesity, metabolic syndrome, diabetes, sleep disturbance and anaemia, have no evident pathophysiological relationship with COPD. The common ground between most of these extrapulmonary manifestations is chronic systemic inflammation.

All of these diseases potentiate the morbidity of COPD, leading to increased hospitalisations and healthcare costs. They can frequently cause death, independently of respiratory failure. Comorbidities make the management of COPD difficult and need to be evaluated and treated adequately.



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Extrapulmonary comorbidities are common in COPD and influence prognosis; we propose an exhaustive comorbidities review <http://ow.ly/o5Uqu>

Introduction

All the studies conducted agree in predicting that both the morbidity and mortality burden of chronic obstructive pulmonary disease (COPD) is rising. By 2020, COPD is projected to cause over 6 million deaths annually worldwide, thus becoming the third leading cause of death in the world [1]. The general ageing of the world's population is reinforcing this trend, partly due to the fact that the prevalence is higher in age groups >50 years (the average age of patients with COPD is 70 years [2, 3]), and partly because incidence remains high in the elderly. For a male aged >55 years who is free from COPD, the estimated risk of developing COPD over the next 40 years is 24% [4].

Our general understanding of the disease has greatly improved over the past 10 years. Epidemiological studies and large clinical trials have helped us to understand the importance of comorbidities [5, 6]. Greater

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understanding of the pathophysiology of COPD, focused on the concept of systemic inflammation, has also helped to explain the high frequency of major comorbidities (such as cardiovascular, skeletal and nutritional disorders) in addition to coexisting conditions that one would naturally expect due to the patients' advanced age and due to shared risk factors. This article reviews the major comorbidities encountered in patients with COPD.

Cardiovascular comorbidities

Heart disease and systemic and pulmonary vascular diseases in COPD

Vascular and heart diseases are among the most important comorbidities observed in COPD, because they have a direct impact on patient survival. The pathophysiological mechanisms underlying the vascular alterations observed in COPD appear to be mainly mediated by endothelial dysfunction and coagulopathy.

Endothelial dysfunction and COPD

The systemic inflammation observed in COPD seems to be the key determinant for the development of pulmonary [7] and systemic [8] endothelial dysfunction, although the precise pathophysiological mechanisms are unknown. Other factors could be involved in maintaining endothelial integrity, such as circulating endothelial progenitor cells (CEPCs). The number of CEPCs appears to be reduced in the systemic circulation and increased in the pulmonary circulation of patients with COPD [7, 9].

Coagulopathy and COPD

The systemic inflammation present in COPD appears to induce a "pro-coagulant" state. In the basal state, COPD patients exhibit abnormally high levels of tissue factor (tissue factor pro-coagulant activity) and Factor VIIa [10], and their fibrin clots are resistant to lysis [11]. After 2 h of artificial hypoxaemia, compared to non-hypoxic controls, COPD patients have abnormally elevated levels of circulating thrombin–antithrombin complex and prothrombin activation fragments, with a parallel elevation in interleukin (IL)-6 [12].

It was recently discovered that coagulation is altered in patients with COPD: tissue factor pro-coagulant activity and circulating levels of thrombin–antithrombin complex are higher than in control subjects, constituting a prothrombotic and pro-inflammatory state that increases the risk of stroke [10]. An electron microscopy study showed that fibrin clots isolated from the plasma of COPD patients are denser and more resistant to lysis than those from control subjects with an equivalent circulating fibrinogen concentration [11]. The same study showed that the fibrin clots from COPD patients became similar to those from subjects without COPD after 3 months of simvastatin treatment.

Systemic venous thromboembolism and COPD

The three factors of Virchow's triad are observed in COPD (systemic venous endothelial dysfunction, coagulopathy and venous stasis due to a physical inactivity), which explains their predisposition to venous thromboembolism (VTE). During COPD exacerbations, VTE is found in 3–29% of cases [13, 14]. There are no specific clinical, biological or radiological signs indicative of VTE, but it should be suspected during COPD exacerbation in the presence of chest pain or syncope, or a fall in arterial carbon dioxide tension in a patient who is usually hypercapnic. VTE during a COPD exacerbation prolongs hospitalisation by 4.4 days and increases the 1-year mortality rate by 30% [14]. Failure to diagnose VTE and to institute suitable anticoagulant therapy increases the death rate by 25% during hospitalisation.

Pulmonary artery disease and COPD: pulmonary hypertension

Pulmonary artery remodelling is observed early in COPD and leads to pulmonary hypertension (PH). This remodelling is the consequence of endothelial dysfunction and coagulopathy, but also of lung-specific mechanisms, such as hypoxic vasoconstriction, destruction of the pulmonary capillary bed by emphysema, smoking-induced inflammatory infiltration of the vascular wall, and shear stress due to redistribution of the blood flow [15]. PH is defined by a mean pulmonary artery pressure (mP_{pa}) >25 mmHg associated with a pulmonary artery occlusion pressure <15 mmHg and by a pulmonary vascular resistance (PVR) >3 Wood units. The prevalence of PH in COPD is ~ 5 –40% [15, 16]. But moderate and severe PH (defined by an mP_{pa} >35 mmHg and >45 mmHg, respectively) only account for ~ 5 % of cases in hospital-based patient series. The presence of PH in COPD worsens gas exchange and dyspnoea, and predisposes to right ventricular (RV) dysfunction and peripheral oedema. It is also associated with higher mortality [17–19].

PH should be suspected in a COPD patient with dyspnoea, desaturation during the 6-min walk test or a disproportionate reduction in the diffusing capacity of the lung for carbon monoxide relative to the severity of the obstruction, or clinical or biological (brain natriuretic peptide) signs of RV dysfunction, not explained by either left ventricular failure or a loud second heart sound in the pulmonic area.

On echocardiography, a high maximum tricuspid regurgitation velocity ($TR_{max} > 3.5 \text{ m}\cdot\text{s}^{-1}$) is suggestive of PH, but TR_{max} cannot be evaluated in one-third of COPD patients due to the low echogenicity of emphysematous lungs [20]. Cardiac catheterisation remains the only examination that can be used to confirm the diagnosis of PH and assess its severity. The presence of PH has little impact on the therapeutic management of COPD. Only long-term oxygen therapy has been shown to be beneficial, which stabilises PH in certain patients with COPD [21].

Coronary heart disease and COPD

Epidemiological association

Coronary heart disease and COPD share the same main risk factor, *i.e.* smoking. The strong epidemiological link between the two diseases is therefore unsurprising. The presence of symptoms of simple chronic bronchitis increases the risk of death due to a coronary event by 50%. The impact of obstructive airway disease, defined by a decrease in the ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC), is less clear-cut, as it only increases the risk of a coronary event by 30%. However, for every 10% decrease in FEV₁, all-cause mortality increases by 14%, cardiovascular mortality increases by 28% and the frequency of non-fatal coronary events increases by 20%. The link between COPD and coronary heart disease is independent of any other confounding coronary risk factors, namely smoking status, cholesterol, systemic hypertension and body mass index (BMI) [22].

Shared pathophysiological mechanisms

Coronary heart disease and COPD are both inflammatory diseases and both involve clotting abnormalities. This phenomenon has long been known for coronary heart disease, and was demonstrated much more recently in COPD (see previously).

In coronary heart disease, the activation of immune cells in the atheromatous plaque induces the production of cytokines such as interferon- γ , IL-1, tumour necrosis factor (TNF)- α , IL-6 and acute-phase inflammatory proteins (fibrinogen, C-reactive protein (CRP) and amyloid protein) [23]. The same mediators are involved in the inflammatory reaction observed in the bronchus in COPD. In addition to these shared pathophysiological determinants, the presence of COPD could contribute to the development of cardiovascular disease through hypoxia, systemic inflammation and oxidative stress [24], and through impaired vasodilatory capacity, as has been shown in the brachial arteries [25].

Coexistence of COPD and coronary heart disease worsens the prognosis of both diseases

Coronary heart disease often goes unrecognised in COPD. A retrospective study of the medical records of 897 COPD patients treated between 2000 and 2003 was conducted in Akershus University Hospital (Oslo, Norway) [26]. The records of 827 (92%) patients included an ECG. Sequelae of myocardial infarction were found on the ECGs of 229 (27.6%) patients, yet only 30% of these patients had a recognised history of myocardial infarction. Follow-up of the cohort until 2005 revealed the negative impact of a high ECG-based cardiac infarction injury score on their survival.

COPD is associated with a systemic inflammatory response and, in particular, with CRP elevation, the concentration of which increases with the severity of the bronchial obstruction. This systemic inflammatory reaction might play a role in the increased coronary risk in patients with COPD [27]. The effect of COPD medication on cardiovascular events is not yet completely clear. The analysis of the data collected during the TORCH (Towards a Revolution in COPD Health) study showed no increase in cardiovascular events in patients with moderate-to-severe COPD receiving salmeterol alone or in combination with oral steroid therapy [28]. The possibility that tiotropium provokes cardiovascular adverse effects continues to be raised [29], with a relationship between the dose placed in the inhaler and the risk of adverse effects having recently been suggested [30].

Heart failure and COPD

Heart failure and COPD are diseases with very similar risk factors, particularly through the role of smoking, that share pathophysiological mechanisms, such as inflammation and skeletal muscle alterations. This explains the frequent coexistence of the two conditions [31], the underestimation of which can lead to delayed diagnosis, given the similarity of the symptoms and to treatment inefficacy.

Heart failure in patients with COPD

In a recent study, transthoracic echocardiography was prospectively performed in 342 COPD patients 3 months after their first exacerbation. Significant cardiac alterations were present in 64% of patients: 27% left- and/or 48% right-heart disorders. In 63% of these patients, cardiac disease was not known [32].

A meta-analysis of 12 analysable studies, published in 2006, in which heart failure was defined as a combination of typical clinical symptoms and a left ventricular ejection fraction of <50%, confirmed that the prevalence of the coexistence of these conditions varies with the stability of the COPD [33]. The prevalence among patients experiencing an exacerbation was as high as 46% *versus* 3.8–16% in those with stable disease. The importance of this combination was confirmed in a cohort study including >45 000 patients with COPD and a sex- and age-matched healthy population of the same size, whose end-points were hospitalisation and cardiovascular mortality rates over a follow-up period of almost 3 years [34]. In terms of relative risk, after adjustment for confounding factors and pre-existing cardiovascular disease, heart failure was the leading cause of hospitalisation and death during the study period. The correlation was stronger in subjects aged <65 years. These results were confirmed in a more recent study on a smaller population (1927 patients) recently diagnosed with COPD and followed for over 5 years [35]. After adjustment for age and sex, the risk of heart failure and death was significantly higher in patients with COPD than in healthy subjects from a database compiled from the general population.

Impact of COPD on heart failure

There are few data on the impact of COPD in patients with heart failure. One of the first studies followed 800 patients with heart failure for 5 years and showed that survival was significantly lower in the group with concomitant COPD. Recent studies on this relationship have corroborated this initial analysis. The studies based on the Norwegian Heart Failure Registry, including 4132 patients with heart failure from 22 cardiology centres, followed for nearly 8 years, demonstrated a significantly higher proportion of deaths in patients with concomitant COPD (32.6% *versus* 37.0%; $p=0.03$) [36]. At baseline, β -blocker therapy was less frequent among patients in the COPD group than in COPD-free patients with identical cardiopathy. This is regularly reported in the literature and should be specifically addressed, given the major role of β -blockers in improving the prognosis of heart failure. There were no data on COPD severity in this cohort, but the results of a less recent study on a smaller number of patients with heart failure are particularly interesting because they took into account the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades of patients with concomitant COPD [37]. Indeed, whereas COPD status was not associated with a significant increase in mortality over the 14.2 ± 8.8 months of follow-up, the survival curves for the various stages of COPD severity revealed that survival among patients with GOLD grades 3 or 4 was significantly lower.

COPD therefore appears to be a truly independent risk factor for death in compromised heart failure patients, and the coexistence of COPD can delay the diagnosis of heart failure. The other causes may be related to the increased risk of non-cardiac death in heart failure patients, infection, or the risk that the coexistence of COPD and heart failure worsens right ventricular dysfunction. The role of β -blockers must also be taken into account. They are known to improve the survival of patients with heart failure, yet are commonly underused in patients with COPD, due to concerns that they will worsen the airway obstruction. Patients are therefore denied the full benefit of heart failure treatments. The use of non-selective β -blockers, which have similar affinity for β_1 and β_2 receptors, is generally accompanied by a reduction in FEV₁, but this is well tolerated in most cases [38]. Switching to a cardioselective β -blocker improves spirometric values, without affecting the left ventricular ejection fraction or New York Heart Association functional class, enabling a better cardiac prognosis without the risk of compromising respiratory function.

The prevalence of heart failure increases with age: eight cases out of 1000 persons for a 50-year-old and 10% after the age of 80 years [39]. Heart failure has been demonstrated to worsen the prognosis of COPD [40].

Lung cancer

Epidemiology

Several epidemiological studies have demonstrated a link between COPD and lung cancer. The prevalence of COPD among lung cancer patients ranges from 40% to 70%, depending on the study [41, 42]. The prevalence of COPD of GOLD grade 2 or higher in a cohort of patients with lung cancer was 50%, compared to 8% in a cohort of smokers without lung cancer (OR 11.6). The annual incidence of lung cancer was at least four times higher in a cohort of patients with COPD than in the general population [43]. While MANNINO *et al.* [44] demonstrated a risk proportional to the severity of the airway obstruction, DE TORRES *et al.* [45] very recently showed that the least severe stages of COPD are associated with a greater risk for developing lung cancer.

Patients with COPD at the time of lung cancer diagnosis have a poorer prognosis [43]: 3-year survival in the COPD-lung cancer group was 15% *versus* 26% in the lung cancer without COPD group (fig. 1). Similarly, an increase in death due to lung cancer was found in nonsmokers with emphysema (HR 1.66) and in nonsmokers with both emphysema and chronic bronchitis (HR 2.44) [46].

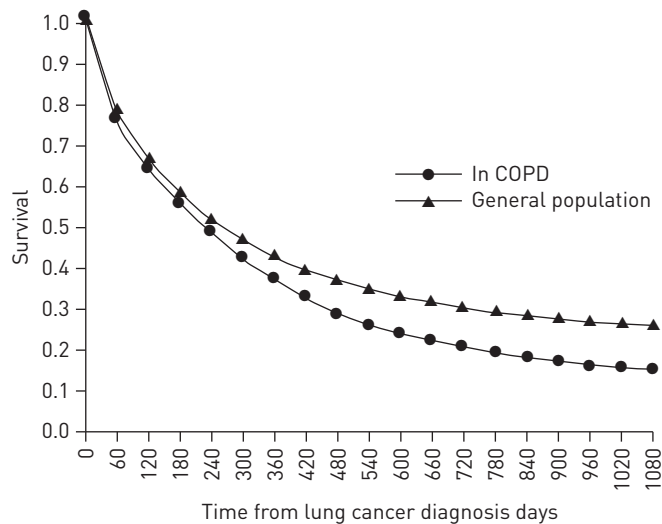


FIGURE 1 3-year survival of lung cancer patients in the general population and in those with a prior diagnosis of chronic obstructive pulmonary disease (COPD). COPD is a negative predictor of survival in lung cancer patients. Reproduced from [43] with permission from the publisher.

Pathophysiology

The mechanisms that predispose COPD patients to lung cancer are not yet fully elucidated [47]. There are currently two main hypotheses.

Shared genetic links that predispose to both diseases

A genetic risk factor common to both of these diseases, combined with the risk related to smoking, was first suggested in 1977 by COHEN *et al.* [48]. Very recently, genome analyses of patients with COPD and lung cancer have shown susceptibility loci common to both diseases on several chromosomes (*e.g.* 15q25, 4q31 and 6p21) [49]. Many susceptibility genes shared by both diseases have been identified, with roles in detoxification, extracellular matrix remodelling (particularly matrix metalloproteinases (MMPs) such as MMP1), DNA repair, cell proliferation and tumour suppression [50]. Conversely, two genetic variants of the 4q31 locus appear to confer protection against COPD and lung cancer in smokers [51]. Finally, a role for epigenetic changes common to the development of lung cancer and COPD has also been suggested. For example, modifications such as DNA methylation, deacetylation of histone proteins and protein phosphorylation have been shown to be involved in the pathogenesis of both diseases [52].

The role of chronic inflammation

Epithelial-to-mesenchymal transition (EMT), in which cells with an epithelial phenotype acquire a mesenchymal phenotype, is known to have an important role in carcinogenesis [52]. Bronchial inflammation itself promotes such EMT. Many factors are shared by these two diseases, such as activation of transforming growth factor- β and of the receptor tyrosine kinase/RaS pathway. Similarly, the transcription factor nuclear factor (NF)- κ B is a key protein in the pathogenesis and development of COPD, enhancing the release of pro-inflammatory mediators. Genes that regulate NF- κ B have also been implicated in tumour development and metastasis. In addition, inhibitors of NF- κ B have been shown to improve the efficacy of first-line therapy in lung cancer patients with COPD [53].

Screening

To our knowledge, there is no specific recommendation to screen for lung cancer in patients with COPD. Recent data from the American National Lung Screening Trial [54] showed a 20% reduction in death due to lung cancer in the group screened using computed tomography compared to the group screened by radiography, among smokers or former smokers aged between 55 years and 74 years with a smoking history of ≥ 30 pack-years. The patients' lung function was not reported in the trial. These epidemiological data suggest that targeted lung cancer screening for COPD patients could be worthwhile. The value of targeted screening for patients with severe disease (GOLD grade 3 or 4) could be investigated in a clinical trial.

A respiratory workup is recommended at the time of diagnosis of localised or locally advanced lung cancer, including at least lung function tests [55]. It is important because COPD severity has an impact on treatment. The local or regional treatment chosen (lung resection, external beam radiotherapy or radiofrequency ablation) depends, in part, on the patient's lung function.

There is no recommendation to screen for the presence of airway obstruction in metastatic lung cancer. The issue is whether COPD treatment would improve the quality of life or even the survival of the patient.

Severe COPD, especially at the stage of chronic respiratory failure, can affect performance status. Performance status must be maintained for chemotherapy to be initiated and is one of the key factors when deciding which cytolytic therapy to use.

Preventing lung cancer in COPD

Smoking cessation is the cornerstone of COPD management. It is the main way of stopping the progression of COPD and of minimising the risk of developing lung cancer.

Pharmacological treatments (nicotine replacement therapy, bupropion and varenicline) and cognitive behavioural therapy have been shown to be effective in increasing the chances of successful cessation for COPD patients [56–58]. Two retrospective cohort studies suggest that inhaled corticosteroids may be protective against lung cancer [59, 60]. A dose–response relationship has been observed between exposure to inhaled corticosteroids and the reduction in the risk of lung cancer. Only high doses of inhaled corticosteroids appear to significantly decrease the risk of lung cancer. Their protective effect is assumed to be based on their anti-inflammatory action. In animal models, they reduce the risk of oncogenesis in bronchopulmonary tissues [61].

A role for physical activity in cancer prevention has also been postulated. Using multivariate analysis of a cohort followed for over 12 years, SPRAGUE *et al.* [62] demonstrated that the risk of developing lung cancer was 45% lower in one-third of the population (4831 subjects) with the highest levels of physical activity than in the third with the lowest levels of physical activity, particularly among the subpopulation of active smokers. The authors did not evaluate the subjects' lung function, so no conclusions can, as yet, be drawn on the benefit of physical activity in the prevention of lung cancer in the COPD subpopulation. To our knowledge, there are no other data, particularly on the effect of a long-term exercise retraining programme on the incidence of lung cancer in COPD patients.

Anxiety and depression disorders

Anxiety is defined by a feeling of indefinable insecurity, which characterises the psychological component of anxiety disorders. Depression, which comes from the Latin *depressio* meaning “press down”, denotes an illness for some or a syndrome for others, whose central manifestation is a mental state characterised by marked lassitude, reduced self-esteem and pessimism. These disorders are common in COPD, anxiety and dyspnoea are closely linked, and depression is more frequent in COPD than in other chronic diseases.

One study suggested that the first hospitalisation for COPD occurs sooner in patients with concomitant anxiety and/or depression. One hypothesis is that dyspnoea might be perceived more intensely and earlier in these patients [63].

Similarly, proven airway obstruction is associated with a higher frequency of generalised anxiety disorder or panic disorder [64]. Depression affects between 20% and 60% of COPD patients depending on the study, COPD stage and the scale used [65–67]. The mortality and readmission rate among anxious and/or depressive COPD patients increases during the 30 days following hospitalisation [68]. The presence of depression has prognostic value, as shown in a study in COPD patients hospitalised for exacerbation [69]. Mortality following a COPD exacerbation was greater among the depressive patients. A simple questionnaire has been validated as a rapid screening instrument for anxiety and depressive disorders [70].

Depression is also a common comorbidity in the elderly population. Its prevalence is 1–5% among ambulatory patients, 13% among institutionalised patients [71] and 40% in patients with respiratory failure. YOANNES *et al.* [72] showed that the rate of depression in a group of 96 elderly COPD patients was significantly higher than in healthy or otherwise disabled elderly subjects.

The Hospital Anxiety and Depression (HAD) scale is an easy-to-use self-report questionnaire that can be helpful in routine practice. It has 14 questions in total and takes about 10 min to complete [73]. The "anxiety" score is obtained by adding the scores from questions 1, 4, 6, 8, 10, 12 and 14. The "depression" score is obtained by adding the scores from questions 2, 3, 5, 7, 9, 11 and 13. For each item, a score strictly >10 indicates an abnormal state of anxiety and/or a high probability of depression. The scale has also been validated in French. However, doctor–patient relationship is essential to assess the psychological impact of the disorder.

Occasionally, medical therapy is necessary. Antidepressants alter the perception of symptoms, such as dyspnoea, and improve quality of life. Therapeutic patient education as part of respiratory rehabilitation may suffice for minor disorders.

Cognitive impairment

A study published in 2006 on 134 patients followed for 32 months evaluated cognitive performance by the ability to copy a simple drawing. The presence of cognitive impairment could be an independent risk factor for mortality (fig. 2) [74].

Osteoporosis

Definition and epidemiology

Osteoporosis is characterised by decreased skeletal resistance through deterioration of the microarchitecture of bone tissue, leading to reduced bone mass and lower mineral content. The consequences are bone fragility and increased fracture risk. It is currently defined by a bone mineral density $\geq 2.5SD$ below the mean for young adults (T-score ≤ -2.5), as measured by bone densitometry. Osteoporosis-related fractures preferentially affect the spine, hip and wrist. Osteopenia corresponds to a "preclinical" stage and is defined as a T-score of between -2.5 and -1 . The prevalence of bone disorders increases with the age: it is estimated that 8–18% of females and 5–6% of males >50 years of age have osteoporosis [75]. As COPD is a disorder of the second half of life, this comorbidity is to be expected. The respiratory complications of osteoporosis are even more marked in COPD because they exacerbate the pre-existing physical inactivity and increase the risk of vertebral fractures, with total lung capacity becoming progressively reduced as the number of vertebral fractures increases. These fractures can also lead to kyphosis, which restricts inhalation movements and reduces lung function parameters (9% reduction in FVC per fracture, and reduced FEV₁).

Epidemiological studies show that the prevalence of osteoporosis in COPD patients is increased. GRAAT-VERBBOM *et al.* [76] conducted a systematic review of 13 cross-sectional studies published between 1998 and 2008, including a total of 775 COPD patients. The analytical methods and definitions of osteoporosis varied between the studies. According to the World Health Organization definition and based on bone densitometry, the prevalence of osteoporosis ranged from 24% to 69%. The COPD patients with osteoporosis had significantly lower FEV₁ and BMI values than those without osteoporosis. There is a negative correlation between osteoporosis and FEV₁ values. Some therapeutic trials include a placebo arm to take into account the natural course; the duration of these trials was nevertheless limited to a few years. SCANLON *et al.* [77] showed a significant reduction in bone density over 3 years in the triamcinolone-treated group (-1.66 ± 4.4), but not in the placebo group (0.1 ± 4.04). 24% of the patients in a subgroup of the TORCH study had osteoporosis at the time of trial entry [78]; after 3 years, the changes in bone density were small and similar in all of the groups, as was the incidence of bone fractures. Finally, a study by MINEO *et al.* [79] evaluated the bone density of 40 patients before and 1 year after lung volume reduction

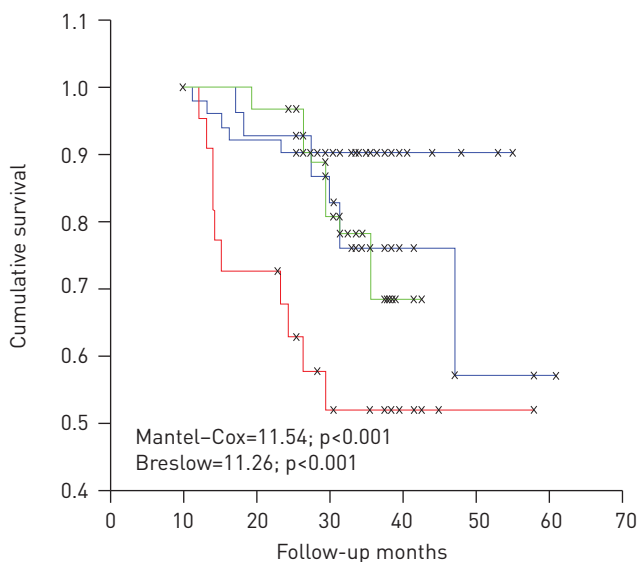


FIGURE 2 Evaluation of cognitive performance based on the ability to copy a simple drawing. Cognitive impairment is a negative predictor of survival in chronic obstructive pulmonary disease patients. Black line: normal copying drawings with landmarks and no hypoxaemia; blue line: normal copying drawings with landmarks and hypoxaemia; green line: impaired copying drawings with landmarks and no hypoxaemia; red line: impaired copying drawings with landmarks and hypoxaemia. Reproduced from [74] with permission from the publisher.

surgery for emphysema. It suggested that this surgery improved bone density, despite oral steroid therapy, which was maintained after surgery in over half of the patients.

The prevalence of even asymptomatic vertebral fractures in COPD patients is of concern, if only because it accelerates their declining lung function. In the Evaluation of Obstructive Lung Disease and Osteoporosis (EOLO) study, the prevalence of vertebral fractures in an ambulatory COPD population was 41%, and correlated with COPD severity [80].

Pathophysiology

Pathophysiological evidence supports the epidemiological observations and sheds light on the potential relationships between the two conditions.

At the cellular level, bone remodelling is regulated by three effectors: 1) the osteoblasts that form the bone matrix, which is subsequently calcified; 2) the osteoclasts that resorb bone; and 3) the osteocytes that coordinate bone remodelling. In addition, three regulatory pathways control the interactions between osteoblasts and osteoclasts.

The first involves direct interaction between these two cells *via* the receptor activator of NF- κ B ligand (RANKL) present at the surface of osteoblasts and its receptor RANK at the surface of pro-osteoclasts, enabling the latter to differentiate into activated osteoclasts. The second pathway involved osteoprotegerin, a protein secreted by stromal cells and osteoblasts. It blocks the interaction between RANK and RANKL, reducing bone resorption. Finally, the Wnt/ β -catenin regulatory pathway downstream of osteoblast activators remains poorly understood.

Risk factors

The known shared risk factors for COPD and osteoporosis are interlinked. Smoking and systemic inflammation affect RANK/RANKL binding, and vitamin D deficiency stimulates parathormone secretion and affects osteoclast maturation through its effect on RANK/RANKL. Recent data show that inflammatory cytokines can also target Wnt. Vitamin D can also improve the expression of the osteoprotegerin/RANKL complex, reducing osteoclast formation. Oral steroid therapy affects bone homeostasis through increased expression of RANKL, decreased osteoprotegerin and suppression of osteoclast apoptosis. The hypogonadism present in COPD also plays a part in the development of osteoporosis: the drop in oestrogen levels inhibits the action of the osteoprotegerin/RANKL complex.

Although an association between smoking and osteoporosis has been established, the studies do not report lung function values [81]. The lower levels of physical activity commonly found in COPD patients have a negative effect on bone metabolism, a phenomenon that has been clearly demonstrated in post-menopausal females. A negative impact of vitamin D deficiency on bone homeostasis has been suggested: its frequency increases with COPD stage, reaching 77% for the very severe stage according to JANSSENS *et al.* [82]. More generally, malnutrition has a negative impact and is another common finding in COPD. The importance of the harmful effect of systemic inflammation, related to COPD severity, has been highlighted previously [83]: pro-inflammatory cytokines, such as IL-1 β , IL-6 and TNF- α , may promote bone resorption. The harmful effect of oral steroid therapy on bone metabolism has long been established, and recent studies of the underlying mechanism have highlighted the impact of oral steroid therapy on both bone resorption and impaired bone formation.

Treatment and prevention

The treatment and prevention of osteoporosis in COPD patients requires non-pharmacological measures. Besides smoking cessation, which is crucial, the chief measure is respiratory rehabilitation: it has been shown in exercise retraining programmes to improve bone mineral density. Such data are lacking in COPD patients, although the indirect effects of such programmes improve muscle strength and balance, and reduce the risk of falling.

Calcium and vitamin D supplementation have proven effective in reducing fracture risk, the effect being dose-dependent for vitamin D and only when combined with calcium [84]. Several recent studies on vitamin D have found it to improve muscle function and postural stability, and to have immunomodulatory effects. A daily dose of 800 IU of vitamin D combined with calcium supplementation is recommended for patients with a T-score of < -1 and three minor risk factors (BMI < 21 kg·m $^{-2}$, active smoking, chronic alcohol abuse, age > 65 years, hip fracture, rib fracture, menopause, sedentary lifestyle and FEV $_1$ $< 50\%$ predicted) or one major risk factor (systemic corticosteroid therapy for > 3 months per year, previous vertebral compression fracture). Bisphosphonate therapy has not been specifically evaluated for osteoporosis in COPD patients, although research by SMITH *et al.* [85] suggests it has a beneficial effect on the T-scores of patients with airways disease. The usefulness in COPD of new treatments such as

teriparatide remains to be defined, whereas its role in the treatment of glucocorticoid-induced osteoporosis is now well established [86].

Malnutrition

Definition

In COPD, patients are usually said to be malnourished when their BMI is $<20 \text{ kg}\cdot\text{m}^{-2}$. Malnutrition reduces the lean body mass (muscle). Lean body mass can be evaluated by dual-energy absorptiometry (expensive equipment), by measuring skin fold thickness (often inappropriate in elderly subjects) or by bioelectrical impedance analysis. The latter method tends to be preferred in routine practice.

Three malnutrition profiles can be identified in COPD: underweight patients with concomitant depletion of lean body mass (60%), underweight patients with a normal lean body mass (20%) and patients of stable body weight with depletion of lean body mass [87].

The importance of considering nutritional status is underlined by the prognostic power of the BODE (BMI, airflow obstruction, dyspnoea and exercise capacity) index [88], which takes into account FEV₁, 6-min walking distance, dyspnoea and BMI.

Pathophysiology

Malnutrition in COPD is the consequence of an imbalance between energy intake and consumption. Inadequate intake is caused by dyspnoea resulting from the effort of eating and by impaired leptin regulation, a hormone that reduces food intake [89]. The reasons for increased energy consumption are unclear but include work of breathing, smoking and medication, including theophylline and β -blockers. Other factors, such as increased protein catabolism due to systemic inflammation, hypoandrogenism and hypoxia, also seem to be involved.

Prevalence

The prevalence depends on COPD stage and the definition of nutritional status used. At the chronic respiratory failure stage, 17% of patients have a BMI $<20 \text{ kg}\cdot\text{m}^{-2}$ [90]. In the Danish cohort [91], 0–5% of patients with GOLD grade 0–2 COPD had a BMI $<18.5 \text{ kg}\cdot\text{m}^{-2}$ versus 15–30% of patients with grade 4 disease. In this study, malnutrition was more marked in females than males, irrespective of COPD stage.

Morbidity and mortality

Several European cohort studies (table 1) have shown a link between malnutrition and mortality [91–95]. In the Danish cohort, for patients with an FEV₁ $<50\%$ pred the relative risk for death was a HR of 1.62 (95% CI 1.15–2.31) for a BMI $<20 \text{ kg}\cdot\text{m}^{-2}$ and 0.62 (95% CI 0.41–0.94) for patients with a BMI $\geq 30 \text{ kg}\cdot\text{m}^{-2}$.

Nutritional rehabilitation

After diagnosing malnutrition, the treatment options available to clinicians are: physical exercise as part of respiratory rehabilitation; caloric, protein and polyunsaturated fatty acid supplementation [96–99]; and anabolic steroids [100, 101].

These approaches can be integrated in a standardised programme. The term nutritional rehabilitation was proposed by SCHOLS [102] and taken up by others [103].

Obesity

There are few factual data on the link between obesity and COPD. However, an obesity (or at least overweight) paradox appears to exist. Obesity does not worsen the respiratory function symptoms of COPD [104] and it even has a protective effect in relation to mortality [91, 105], although the picture differs in morbid obesity (BMI $>40 \text{ kg}\cdot\text{m}^{-2}$). JORDAN *et al.* [106] reported a significant increase in deaths due to respiratory disease in subjects with a BMI $>40 \text{ kg}\cdot\text{m}^{-2}$ (HR 5.78, 95% CI 1.09–30.61). Obese patients, especially those with COPD, should be investigated for obstructive sleep apnoea syndrome (OSAS) and obesity hypoventilation syndrome.

Metabolic syndrome and diabetes

Metabolic complications are common comorbidities of COPD, namely type 2 diabetes and metabolic syndrome.

Definitions

Diabetes mellitus is defined by insufficient secretion or effect of insulin. The clinical and laboratory signs of diabetes are polyuria-polydipsia syndrome, blood glucose $>11.1 \text{ mmol}\cdot\text{L}^{-1}$ or a fasting blood glucose

TABLE 1 Studies reporting a link between body mass index (BMI) or body composition and mortality

First author [ref.]	Study	Subjects n	Follow-up	Severity	Mortality
SCHOLS [92]	Single-centre retrospective cohort	412	48 months	Mean FEV ₁ 39%	FFMI predicts mortality independently of BMI, fat mass, age and sex
LANDBO [93]	CCHS prospective cohort	2132	17 years	Mean FEV ₁ 64–66%	Low BMI (<20 kg·m ⁻²) versus normal BMI (20–25) Male: RR 1.64 [95% CI 1.2–2.23] Female: RR 1.42
CHAILLEUX [94]	ANTADIR retrospective cohort	4088	7.5 years (average)	FEV ₁ 630–860 mL LTOT	Low BMI is a risk factor for mortality, independently of age, FEV ₁ , P _{aO₂} and sex
SOLER-CATALUNA [95]	Single-centre prospective cohort	96	3 years	Mean FEV ₁ 44%	Anthropometric measurement of muscle depletion ≤25th percentile associated with higher mortality after 12 months (12% versus 5.9%), 24 months (31% versus 7.9%) and 36 months (39.2% versus 13%)
VESTBO [91]	CCHS prospective cohort	1898	7 years	GOLD 0–IV	Percentage of malnourished subjects is higher in females than males Low BMI increases risk of overall mortality (HR 1.8) and COPD-related mortality (HR 3.2)

CCHS: Copenhagen City Heart Study; ANTADIR: Observatory of Association Nationale pour le Traitement a Domicile de l'Insuffisance Respiratoire Chronique; FEV₁: forced expiratory volume in 1 s; LTOT: long-term oxygen therapy; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FFMI: fat-free mass index; RR: relative risk; P_{aO₂}: arterial oxygen tension; HR: hazard ratio; COPD: chronic obstructive pulmonary disease.

>7 mmol·L⁻¹, a 2-h post-prandial blood glucose >11.1 mmol·L⁻¹ with HbA_{1c} ≥6.5%. The definitions of metabolic syndrome are summarised in table 2 [109].

Epidemiology

The prevalence of diabetes in COPD patients varies between studies: 10.3% in a population of grade 2/3 COPD patients in a rehabilitation centre according to CRISAFULLI *et al.* [4], 12.6–14.5% in an all-stage COPD population according to MANNINO *et al.* [110], 12.2% with an increased risk in active smokers according to FEARY *et al.* [111] and 18.7% according to CAZZOLA *et al.* [112]. The prevalence of metabolic syndrome is 22.5% for all grades according to GHANASSIA *et al.* [113], and 53% for GOLD grade 2 COPD, 37% for GOLD grade 3 COPD and 44% for GOLD grade 4 COPD according to WATZ *et al.* [114]. In the latter study, the presence of metabolic syndrome was associated with higher levels of the markers of systemic inflammation, CRP and IL-6.

TABLE 2 Definitions of metabolic syndrome according to the World Health Organization (WHO) and the International Diabetes Federation (IDF)

Criterion	WHO definition [107] [#]	IDF definition [108] [†]
Blood glucose	≥1.1 g·L ⁻¹ or impaired glucose tolerance or specific treatment	≥1 g·L ⁻¹ or specific treatment
Plasma triglycerides	≥1.5 g·L ⁻¹	≥1.5 g·L ⁻¹
HDL cholesterol	<0.35 g·L ⁻¹ for males and <0.39 g·L ⁻¹ for females or specific treatment	<0.4 g·L ⁻¹ for males and <0.5 g·L ⁻¹ for females or specific treatment
Abdominal (central) obesity	Waist circumference/hip circumference ratio >0.9 for males and >0.85 for females and/or BMI >30 kg·m ⁻²	Waist circumference ≥94 cm for males and ≥80 cm for females for Europids
Blood pressure	SBP ≥140 mmHg or DBP ≥90 mmHg or antihypertensive treatment	SBP >130 mmHg or DBP >85 mmHg or antihypertensive treatment
Urinary albumin excretion rate	≥20 µg·min ⁻¹ or ≥30 mg·g ⁻¹ creatinine	

HDL: high-density lipoprotein; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. #: diabetes with two other criteria; †: abdominal obesity with two other criteria.

Cohort studies have shown that moderate to severe COPD increases the risk of diabetes (OR 1.4 and 1.5, respectively) [110]. In a large cohort of females, SONG *et al.* [115] showed that the presence of asthma or COPD was associated with a risk of developing type 2 diabetes, suggesting that airway inflammation contributes to the pathophysiology of diabetes. Conversely, in a US cohort, the relative risk of developing COPD was higher (HR 1.22) in patients with diabetes than in non-diabetics [116].

Mortality

Diabetes also affects the prognosis of COPD (time to first hospitalisation and 5-year mortality rate) [110]. According to the Emerging Risk Factors Collaboration [117], the HR for COPD-related death was 1.27 compared to subjects without diabetes. BAKER *et al.* [118] showed that an increase in blood glucose of 1 mmol·L⁻¹ increases the risk of death by 15%. PARRAPIL *et al.* [119] confirmed an increased risk of death (OR 1.93) and hospital stays were 10.3% longer for patients with diabetes hospitalised for COPD exacerbation.

Pathophysiology

Systemic inflammation (with elevated markers such as CRP, TNF- α and IL-6) plays an important role in both the progression of COPD and the development of insulin resistance. Smoking is one cause of inflammation, which may explain the data reported by FEARY *et al.* [111] and MANSON *et al.* [120]: smokers have a two-fold higher risk of developing diabetes than nonsmokers.

A recent review of the literature demonstrated the complex link between smoking and obesity in the development of comorbidities, involving an enzyme cascade that originates in adipose tissue considered a site for production of cytokines (TNF- α , IL-6, *etc.*) while adiponectin decreases with increased adiposity. This increases insulin resistance, circulating free radicals and oxidative stress, exacerbating the initial pulmonary inflammation. Adipose tissue stimulation is promoted by tissue hypoxia, smoking and the degree of bronchial obstruction [121–124]. The elevation of inflammatory markers (IL-6, TNF- α , CRP, *etc.*) correlates strongly with weight gain. Metabolic syndrome is also associated with a pro-inflammatory and prothrombotic state [123].

Mechanisms

The pulmonary consequences of diabetes and metabolic syndrome lead to a somewhat restrictive pattern, with significantly lower FEV1 and FVC values than in non-diabetics, even after adjustment for age, sex, BMI, smoking status, diabetes duration and HbA1c levels [125–128]. Two Asian cohort studies, including >7000 patients, investigated metabolic syndrome, showing a link between airway obstruction and central obesity [129, 130]. LEONE *et al.* [128] also found a strong correlation between metabolic syndrome and impaired lung function, which was especially stronger in active smokers or former smokers. Abdominal obesity had a dominant role, and subcutaneous and intra-abdominal adipose tissue correlated with circulating levels of IL-6 and TNF- α , while there was a negative correlation with levels of adiponectin, which plays a role in insulin sensitivity. The mechanisms underlying lung volume restriction could include a combination of abdominal obesity, reduced pulmonary elasticity through non-enzymatic glycosylation of tissue proteins, loss of inspiratory muscle strength and/or diaphragmatic compromise due to diabetic neuropathy. *Post mortem* series also show diffuse thickening of the alveolar membranes and centrilobular emphysema [131].

Impact of treatments

What is the role of the various treatments used in COPD in insulin resistance? The role of β_2 -agonists and oral steroid therapy has already been demonstrated [132]. SUISSA *et al.* [133] confirmed that high-dose inhaled corticosteroids are a risk factor for the development or poor control of diabetes.

When can metformin be used in COPD? The contraindications to metformin are typically renal failure, congestive heart failure, acute or chronic metabolic acidosis, hepatic insufficiency and conditions that may cause tissue hypoxia, such as respiratory failure. Age >80 years, alcohol abuse and concomitant treatment with nephrotoxic drugs are relative contraindications. They are associated with the risk of lactic acidosis [134]. Metformin should also be discontinued in situations where there is a risk of acute renal failure, such as intravascular contrast media (discontinued for 3 days) in radiological studies, sepsis, hepatitis or gastrointestinal disturbances involving diarrhoea and vomiting, or of acute hypoxia, such as during acute cardiac or respiratory failure or perioperatively [135, 136]. However, there is some debate in the literature over the causality of metformin and the contraindications. Several authors have also demonstrated that it is regularly administered to patients who have two or three risk factors [137, 138]. RACHMANI *et al.* [139], whose study included ~40 grade 3 COPD patients in each group, came to the same conclusion, with no harmful consequences. There have been some reports of episodes of lactic acidosis, in which COPD was cited in the history or as a risk factor, but none reported the severity of the COPD [140, 141] and the causes of the acute episode are dominated by acute renal failure, cardiogenic or septic shock and hepatic insufficiency. SCALE and

HARVEY [142] reviewed the 48 cases of lactic acidosis that occurred in patients with type 2 diabetes (out of a total of 149) and looked for predisposing factors: COPD was not mentioned. It appears, therefore, that unless respiratory failure is present, COPD is not a contraindication to metformin therapy.

As regards using statins to treat the dyslipidaemia associated with metabolic syndrome, they may have an anti-inflammatory, antioxidant and immunomodulatory effect [143]. They may also have an effect on pulmonary hypertension in COPD [144, 145]. Treatments for hypertension or heart failure in patients with diabetes (angiotensin-converting enzyme inhibitors, angiotensin II blockers and cardioselective β -blockers) may reduce COPD exacerbations and mortality through an anti-inflammatory effect and by delaying the onset of pulmonary arterial hypertension [144–146].

Sleep disturbance

Epidemiology

Impaired sleep quality is common in COPD. It was first demonstrated in questionnaire-based studies, with or without sleep studies. According to CORMICK *et al.* [147], out of a population of 50 patients with severe COPD, 36% complained of trouble falling asleep, 42% of non-restorative sleep and 76% of more than two prolonged periods of wakefulness per night, while 28% were using hypnotics. Sleep studies confirmed that the total sleep period, total sleep time and non-rapid eye movement (REM) sleep time were reduced, while sleep latency, arousals and the number sleep state changes were increased. According to KLINK *et al.* [148], 35.9% of patients in the TESOAD (Tucson Epidemiologic Study of Chronic Lung Disease) cohort with airway obstruction had sleep disturbances, based on questionnaire data. The risk factors were respiratory symptoms, female sex, increasing age and obesity. DODGE *et al.* [149] showed that for 60% of patients, sleep disturbances persisted between two evaluations separated by an interval of 7 years conducted in the same population, with the incidence of sleep disturbances being increased by the presence of respiratory symptoms and in age groups over 45 years of age.

Impaired sleep quality appears to be more common in patients with severe COPD. The analysis of the Sleep Heart Health Study [150], which focused on patients with moderate COPD, did not find sleep quality or architecture to be significantly impaired in the absence of OSAS, whereas KRACHMAN and co-workers [151, 152] confirmed the data of CORMICK *et al.* [147] in severe COPD. More recently, VALIPOUR *et al.* [153] found that sleep quality was impaired, based on both questionnaire data (the Sleep Disorders Questionnaire: difficulty initiating or maintaining sleep ($p < 0.001$), and sleep problems resembling anxiety and depressive disorder ($p < 0.035$)) and polysomnographic evaluation (reduced total sleep time: 4.7 *versus* 5.5 h ($p < 0.05$); sleep efficacy: 75% *versus* 82% ($p < 0.01$); percentage of REM sleep: 14% *versus* 17% ($p < 0.05$)) in 52 patients with moderate COPD compared to 52 controls. According to BUDHIRAJA *et al.* [154], COPD is a risk factor for insomnia, with an odds ratio of 1.9 (95% CI 1.5–2.5; $p < 0.001$) relative to a control population.

However, excessive daytime sleepiness is not as widespread: 19.5% among patients with obstructive airway disease according to KLINK *et al.* [148], which was not significantly different from patients without airway obstruction, but was more frequent in subjects who regularly snore; while VALIPOUR *et al.* [153] found that the sleepiness scores of COPD patients and controls did not differ significantly.

Mechanisms

There are multiple causes for poor-quality sleep. One hypothesis is distension and increased work of breathing, potentiated when lying down [152, 155], which is supported by the improvement in sleep in patients who have undergone lung volume reduction surgery [156]. Respiratory symptoms (dyspnoea, cough and expectoration) can cause arousal. There is no consensus over the role of nocturnal hypoxia, but there appears to be no correlation between sleep quality (total sleep time and sleep efficacy) and nocturnal arterial oxygen saturation [152, 156, 157].

According to LO COCO *et al.* [158], based on interview data, one-third of COPD patients have restless legs syndrome and 62% of these patients complain of sleep disturbances: periodic limb movement syndrome can contribute to this phenomenon. Anxiety and reactive depression are common in COPD patients and cause sleep disturbances.

Pain can disturb sleep initiation or wake patients during the night: 25.7% of patients reported pain in the Pittsburgh questionnaire in the study by SCHARF *et al.* [159]. Finally, the presence of OSAS exacerbates sleep disturbances in COPD patients [150].

Impact of treatments

Exclusively nocturnal oxygen therapy has not been validated in prospective studies [160, 161]. Long-acting inhaled bronchodilators do not affect sleep quality [162, 163]. Studies on indacaterol suggest that it reduces nocturnal awakenings due to dyspnoea, compared to placebo and comparators (tiotropium and salmeterol)

[164, 165]. Meta-analysis from WIJKSTRA *et al.* [166] concludes that long-term noninvasive ventilation (NIV) does not improve sleep quality in stable severe COPD. Nevertheless, CLINI *et al.* [167] and MCEVOY *et al.* [168] found that NIV combined with oxygen therapy slightly improves the sleep of patients with severe hypercapnic COPD compared to oxygen therapy alone. According to CRISAFULLI *et al.* [169], average volume assured pressure support is as effective and comfortable as fixed ventilation and improves sleep quality.

The main consequences of poor sleep quality are reduced quality of life [170, 171], exacerbation of anxiety and depression, and uncontrolled use of hypnotics, which can be harmful.

The treatment of insomnia in COPD patients involves restricting the time spent in bed, stimulus control, relaxation and cognitive behavioural therapy [172]. Short-term hypnotics can be considered, but not in patients with untreated concomitant OSAS or chronic hypercapnic respiratory failure, or during exacerbations [173, 174].

OSAS and COPD

It is important to consider the possibility of the coexistence of OSAS and COPD, bearing in mind the consequences. OSAS is no more prevalent in COPD than in the general population. According to SANDERS *et al.* [151], in the >40-year-old population of the Sleep Heart Health Study cohort, 22.3% of patients with obstructive airways disease had an apnoea/hypopnoea index (AHI) >10 *versus* 28.9% of others ($p < 0.0001$) and 14% *versus* 18.6% had an AHI >15 ($p < 0.0002$). According to BEDNAREK *et al.* [175], in the MONICA II (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) study, the prevalence of OSAS in a COPD population and COPD-free population did not differ significantly: 11.1% *versus* 17%, respectively, had an AHI >10 (not significant) and 8.3% *versus* 12.2%, respectively, had an AHI >15.

The risk factors for OSAS in COPD patients are the same as in the general population. OSAS should be suspected in the presence of typical nocturnal clinical signs (snoring, breathing pauses noticed by the partner, poor sleep, *etc.*) and daytime signs (non-restorative sleep, headache on awakening, excessive daytime sleepiness), as well as impaired gas exchange or pulmonary hypertension inadequately explained by lung function and blood gas test results. The diagnosis can be confirmed using a type 3 portable monitoring device, with polysomnography rarely being necessary. The OSAS-COPD combination has important consequences: reduced sleep quality, increased nocturnal hypoxaemia and nocturnal desaturation [176, 177], more frequent daytime hypercapnia [176], pulmonary arterial hypertension and more frequent right heart failure than in COPD patients without OSAS or in OSAS patients without COPD [176, 177], higher risk of being admitted into hospital for an exacerbation [178], and higher risk of systemic inflammation and oxidative stress, with additive or synergistic effects playing a role in cardiovascular comorbidities [179]. Finally, the risk of death is increased [178, 180]. Continuous positive airway pressure (CPAP) is the standard treatment for OSAS. It is effective and improves prognosis (fig. 3) [178, 180].

Oxygen therapy is sometimes given in addition to CPAP when nocturnal hypoxaemia persists (mean <90%) or when the usual criteria for instituting long-term oxygen therapy (>16–18 h per 24 h) are met [181]. NIV may be used immediately, depending on the severity of daytime or nocturnal hypoventilation, possibly switching later to CPAP or at a later date if nocturnal hypoventilation (during REM sleep) persists during CPAP therapy. Studies are required to optimise the therapeutic strategy.

Anaemia

Epidemiology

Anaemia is defined by a haemoglobin concentration of <13 g·dL⁻¹ for males and 12 g·dL⁻¹ for females [182]. Anaemia was recently identified as a comorbidity of COPD. Hypoxaemic smokers would actually be expected to exhibit polycythaemia, but studies that have reported haematological values show that anaemia is more common than polycythaemia, with a prevalence ranging from 12.3% to 23% for anaemia and of 6% for polycythaemia [183–185].

Anaemia and systemic inflammation

COPD is a systemic inflammatory disease in which IL-1, IL-6 and TNF- α play a role. Many other chronic diseases with systemic inflammation are associated with anaemia, such as cancers and connective tissue diseases. Elevation of IL-1, IL-6 and TNF- α , which have a harmful effect on erythropoiesis, is also found in these diseases [186]. However, although several authors have demonstrated an association between the presence of anaemia and markers of inflammation such as CRP in COPD patients [187, 188], there is currently no evidence of a direct role for COPD-related inflammation in the anaemia observed.

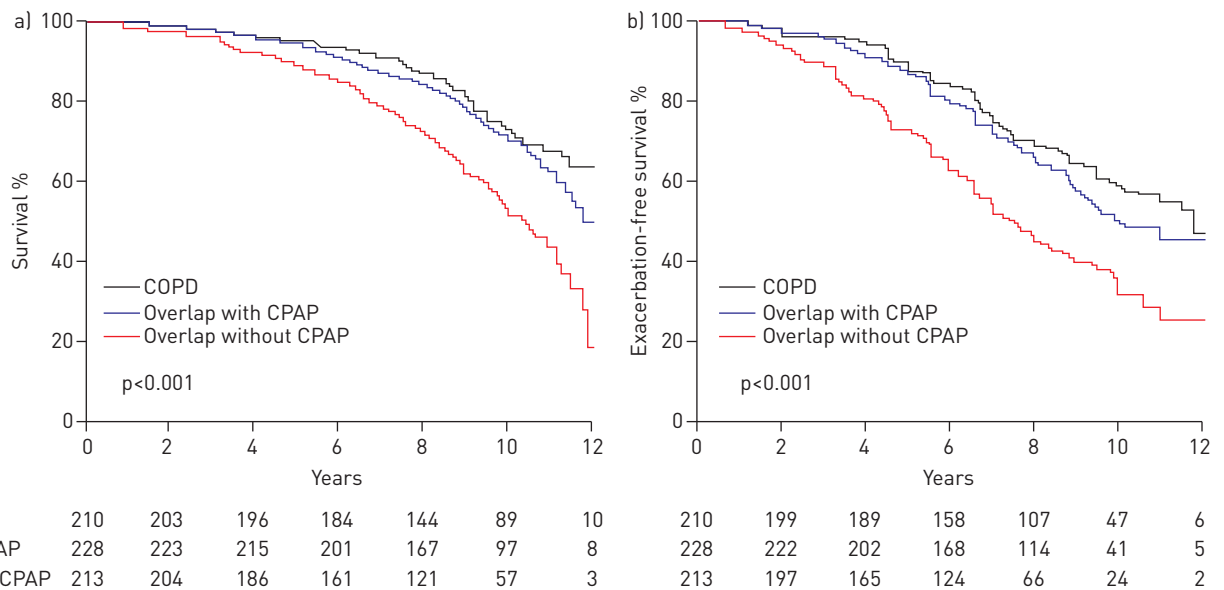


FIGURE 3 Comparison of a) survival and b) exacerbation-free survival in three populations: chronic obstructive pulmonary disease (COPD) alone; COPD with obstructive sleep apnoea syndrome (OSAS) treated with continuous positive airway pressure (CPAP); and COPD with OSAS not treated with CPAP. Reproduced from [178] with permission from the publisher.

Confounding factors

There are many confounding factors associated with COPD, such as old age, malnutrition and cardiovascular disease, which can also be responsible for anaemia. Malnutrition can be associated with iron, folate or vitamin B12 deficiency, all of which can result in anaemia. Anaemia is also a frequent comorbidity in heart failure patients, with a prevalence of 15% [189–192]. It is due to the chronic inflammation associated with heart disease, as well as activation of the renin angiotensin system that causes some degree of haemodilution [192].

There are, therefore, many confounding factors that are very important in the development of anaemia. It is advisable to screen for them in anaemic COPD patients.

The impact of anaemia in COPD

Few studies have looked at the consequences of anaemia on patients with COPD. KRISHNAN *et al.* [193] showed that anaemia is associated with reduced quality of life in COPD patients.

COTE *et al.* [183] studied 683 COPD patients, 116 of whom had a haemoglobin concentration $<13 \text{ g}\cdot\text{dL}^{-1}$. They demonstrated several significant differences in the anaemic patients, independently of age, FEV₁, other comorbidities and BMI. Their dyspnoea score was generally higher. Their exercise capacity was lower, indicated by a shorter 6-min walking distance. Finally, the survival rate of anaemic COPD patients was significantly lower.

The same is true for patients with chronic obstructive respiratory failure. CHAMBELLAN *et al.* [184] studied a cohort of 2524 oxygen-dependent COPD patients. They showed that anaemia was an independent negative predictor of the rate and cumulative duration of hospitalisation and of the survival of COPD patients receiving oxygen therapy.

Anaemia therefore has a negative impact on the prognosis of COPD patients. It also interferes with their treatment, because respiratory rehabilitation is compromised by the patients' reduced exercise capacity. The treatment of anaemia therefore seems to be a possible target for improving the clinical management of COPD.

Treating anaemia in COPD

There are very few studies on this subject. SCHONHOFER *et al.* [194] showed that blood transfusion significantly reduced the work of breathing and improved withdrawal of ventilation in a group of 11 anaemic COPD patients in critical care. The use of erythropoietin (EPO) would be easier to implement in practice. EPO therapy has been studied extensively in heart failure. A recent meta-analysis showed that EPO improves survival in anaemic patients and patients with heart failure [195]. EPO appears to be a promising approach for treating anaemia in chronic diseases, but no studies have yet been conducted in COPD.

Lung fibrosis

Smoking is a common risk factor for lung fibrosis and COPD. In a cohort of 2416 smokers, interstitial lung lesion was found in 8% of case by high-resolution computed tomography [196]. So, the proportion of interstitial lung disease in the smoker population is not negligible and it can be associated with COPD, which is a frequent disease in the same population. Indeed, combined pulmonary fibrosis and emphysema (CPFE) is a clinical syndrome which is now well described.

Pulmonary function tests

Patients with this entity have specific pulmonary function tests. There are characterised by relatively normal spirometry and lung volumes in the setting of severely impaired gas exchange. The normal lung volumes are explained by the inverse effect of the restriction seen in pulmonary fibrosis and the hyperinflation seen in emphysema. The normal spirometry is secondary to the association of bronchus obstruction and collapse in emphysema and inversely airway traction by peribronchial fibrosis. At the same time, reduction of vascular surface in emphysema and the alveolar membrane thickening due to fibrosis combine to reduce gas exchange. This exchange gas reduction explains that CPFE syndrome is characterised by a patient with severe breathless and hypoxaemia.

Computed tomography scan

The CPFE syndrome computed tomography scan is characterised by an upper lobe emphysema and lower lobe pulmonary fibrosis. Bullous, paraseptal and centrilobular emphysema are the most frequent upper lobe abnormalities. In the lower lobe, honeycombing, reticular intralobular opacities and traction bronchiectasis are the most frequent findings. Idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia are the main reported pathological patterns of pulmonary fibrosis [197].

Complications and mortality

Patients with CPFE syndrome have different complications and mortality than those with pulmonary fibrosis or emphysema alone.

PH is the most important morbidity of CPFE. It seems to be more frequent and more severe in CPFE patients than in patients with IPF alone. In a cohort of 40 patients with right heart catheterisation, COTTIN [198] found that a reduced cardiac index or an elevated PVR were predictors of poor prognosis.

Lung cancer is also associated with CPFE. The prevalence appears to be higher in the CPFE population than in the general population or in COPD patients alone [199].

In terms of mortality, patients with CPFE syndrome have a significantly reduced survival compared to COPD patients alone. Median survival in a cohort of patients is ~6 years [194]. Except for lung transplantation, there is no specific treatment that improves patients' median survival.

Comorbidities and COPD exacerbation

In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) cohort, the authors studied 2164 clinically stable COPD patients. They showed that a severe bronchial obstruction was not sufficient to explain COPD exacerbations [200].

To better characterise the COPD patients phenotypes, BURGEL *et al.* [201] used cluster analyses. They defined two COPD patient groups who had frequent exacerbations. The first group had a severe obstructive syndrome. The second group had a moderate obstructive syndrome but also comorbidities. Thus this study suggested that there is a real relationship between comorbidities and exacerbations.

COPD exacerbations impact on comorbidities

We showed in this review that systemic inflammation in COPD is very important in the pathophysiology of all comorbidities. Some studies showed that this inflammation increases during COPD exacerbations with an elevation of oxidative stress, plasma fibrinogen and serum IL-6 levels [202, 203], suggesting that COPD exacerbations can increase comorbidities.

Indeed, some studies suggest that coronary heart disease can be increased by exacerbations. After analysing data from 25 857 patients with COPD over a 2-year period, DONALDSON *et al.* [204] found that the risk of myocardial infarction is increased 2.27-fold during the 5 days following the onset of an exacerbation, defined by the use of steroids or antibiotics.

However, exacerbations can have an impact on osteoporosis and malnutrition of COPD patients. KIYOKAWA *et al.* [205] followed up 42 patients for whom exacerbations were recorded and thoracic vertebral

bone mineral density was measured using chest computed tomography. In this way, they demonstrated that COPD exacerbations are independently associated with osteoporosis progression.

Acute exacerbation of COPD is accompanied by an impaired energy balance due to decreased dietary intake and increased resting energy expenditure. It has a negative consequence on patient's nutritional status after repeated exacerbations [206].

COPD comorbidities impact on exacerbations

The role of venous thromboembolism in causing COPD exacerbation is not well known and it must to be sought to end doubt. Other comorbidities have an impact on exacerbation appearance. In a retrospective *post mortem* analysis of patients who died early during COPD exacerbations, the authors showed that heart failure and lung embolism were the principal causes of death [207].

Other comorbidities linked in less obvious ways to COPD exacerbation have also been studied. Indeed, anxiety was found to be related to increased risk of relapse after exacerbation [208] and hospital readmission [209]. The role of depression on exacerbation is less clear but it has prognostic value because it extends the duration of hospitalisation [69, 210]. In the same way, metabolic syndrome has an impact in exacerbation. According to KÜPELI *et al.* [211], patients with metabolic syndrome had more exacerbations over an 18-month period (2.4 *versus* 0.68, $p < 0.001$). During a COPD exacerbation, hyperglycaemia is associated with a higher risk of prolonged hospitalisation or death than normal blood glucose levels.

Conclusion

In this review we showed that COPD is frequently associated with other diseases. There is consistent evidence that these comorbidities have a greater negative impact in COPD patients in terms of quality of life, exacerbation and mortality. Thus, diagnosis and management of comorbidities is an important challenge for the COPD patient. Consequently, the COPD guidelines take into account these comorbidities. Indeed, the revised GOLD document has included a chapter giving simple advice to the clinician managing patients with COPD and comorbidities. In these guidelines, diseases associated with COPD should be assessed and treated according to usual guidelines, as there is no evidence that comorbidities should be treated differently in the presence of COPD (GOLD). But it is not always easy to diagnose the coexisting illness. Indeed, these can be asymptomatic or the symptoms may not be specific in COPD patient. Thus, systematic research of comorbidities seems to be of interest. BMI, the HAD scale, ECG and chest radiography are easy to obtain in medical practice and should be regularly used to assess COPD patients. Transthoracic echocardiography, bone mineral density assessment and computed tomography should be also performed for clinically significant COPD or when other risk factors are associated.

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