Comorbidities and Systemic Effects of Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. It has been projected to move from the sixth to the third most common cause of death worldwide by 2020, while rising from fourth to third in terms of morbidity within the same time frame.1

The prevalence of COPD in the general population is estimated to be around 1% of the adult population, but rises sharply among those 40 years and older. The prevalence continues to climb appreciably higher with age.2

COPD is known primarily to affect the lung structure and function, resulting in emphysematous destruction of lung tissue and large and small airway disease that occur in varying proportion and severity within individuals.3

Besides the lung abnormalities, COPD is now recognized to be a condition that has an impact on other organs, the so-called systemic effects and comorbidities of COPD.4–6 Conventionally, comorbidity has been defined as a disease coexisting with the primary disease of interest. In COPD, however, the definition becomes more perplexing, as certain coexisting illnesses may be a consequence of the patients’ underlying COPD when it could termed as more of a systemic effect.

It is as yet unclear whether these associations are a consequence of shared risk factors such as cigarette smoking or poor physical activity, or whether COPD is a true causal factor. Nevertheless, these extrapulmonary features of COPD add to the challenge and burden of assessing and managing the disease.

This article reviews the types, possible mechanisms, and clinical implications of these systemic effects and comorbidities on COPD patients.

CLASSIFICATION

Table 1 lists the systemic effects and comorbidities associated with COPD. Table 2 summarizes the results of a PubMed search investigating the prevalence of COPD and comorbidities in various studies performed in the past.

CARDIOVASCULAR DISEASE

COPD is now well known to be a risk factor for the development of atherosclerosis and consequent cardiovascular complications.7,8

KEYWORDS

- Chronic obstructive pulmonary disease
- Comorbidities
- Systemic effects
- Inflammation
- Management strategy

KEY POINTS

- Definitive types of systemic effects and co-morbidities have been seen in COPD patients.
- There are possible contributory mechanisms to these effects.
- There are clinical implications of these co-morbidities in the cohort.
- Novel therapies reduce the burden of observed effects.
Prevalence

Cardiovascular disease is undoubtedly the most significant nonrespiratory contributor to both morbidity and mortality in COPD. In a large cohort of patients with COPD admitted to a Veterans Administration Hospital or clinic, the prevalence of coronary artery disease was 33.6%, appreciably higher than the 27.1% prevalence seen in a matched cohort without COPD.9 In the Lung Health Study,10 which assessed deaths and hospitalizations over a 5-year period in a cohort of COPD patients, mortality in 5887 patients aged 35 to 46 years with COPD with mild to moderate airways obstruction was 2.5%, of whom 25% died of cardiovascular complications. Moreover, in these patients with relatively mild COPD, cardiovascular disease accounted for 42% of the first hospitalization and 44% of the second hospitalization over a follow-up period of 5 years. By comparison, only 14% of the hospitalizations in this cohort were from respiratory causes.

Divo and colleagues11 looked at 1664 patients with COPD over 4 years to evaluate COPD comorbidities and mortality risk. Using a multivariate analysis, they generated a COPD comorbidity index (COPD-specific comorbidity test) based on the comorbidities that increase mortality risk. The prevalence of coronary artery disease in this study was unsurprisingly highest at 30.2%, with congestive heart failure (HF) and dysrhythmias making up another 15.7% and 13% of the cases, respectively, and correlated strongly with the association for increased risk of death (P<.05).

Holguin and colleagues12 assessed the prevalence of COPD deaths in United States between 1979 and 2001, and found approximately 47 million hospital discharges (8.5% of all hospitalizations in adults) with a primary or secondary diagnosis of COPD (21% and 79%, respectively). The reported hospital mortality in this cohort was related to heart disease in 43%, taking the major share for the cause of death, compared with 37% related to respiratory failure and another 25% related to pneumonia.

Forced expiratory volume in 1 second (FEV₁) is also known to be an independent predictor of cardiovascular complications in COPD patients. In the Lung Health Study, for every 10% decrease in FEV₁, cardiovascular mortality increased by approximately 28% and nonfatal coronary events increased by approximately 20% in mild to moderate COPD.13 Even a moderate reduction of expiratory flow volumes multiplies the risk of cardiovascular morbidity and sudden cardiac deaths by 2 to 3 times, independent of other risk factors.13–16

COPD patients also have shown evidence of atherosclerotic plaque burden as assessed by increased carotid intimal medial thickening (CIMT),17 and are associated with increased cardiovascular and all-cause mortality.18

Pathogenesis

The pathogenesis of atherosclerosis in COPD is multifactorial.19 Box 1 summarizes the potential mechanisms that have been linked directly or indirectly to the cardiovascular complications seen in this cohort. Fig. 1 summarizes the presumed mechanisms for cardiovascular disease in COPD patients.

Inflammation

Inflammation is considered to be a potential pathogenic mechanism in atherosclerosis. Recent studies, however, indicate that sustained systemic inflammation occurs only in a proportion of patients with COPD, and its relationship to the development of cardiovascular disease has as yet not been fully established.20 Patients with COPD and coexistent cardiovascular disease nevertheless tend to have higher systemic levels of biomarkers, such as interleukin (IL)-6 and fibrinogen, than those without this comorbidity.21 In addition, systemic inflammation increases exacerbations of COPD when there is an increased risk of cardiovascular events.22,23

The specific cellular mechanisms by which systemic inflammation plays a role in the pathogenesis of cardiovascular disease are complex. However, studies have revealed the importance of inflammation in atherosclerotic plaque initiation, development, and rupture (see Fig. 1).24,25

18F-Fluorodeoxyglucose positron emission tomography imaging has also shown direct evidence of inflammation in the vascular wall of the aorta, presumably associated with atherosclerotic plaques, in patients with COPD when compared with smoking control subjects.25

Table 1

<table>
<thead>
<tr>
<th>Systemic Effects of COPD4–6</th>
<th>Comorbidities in COPD4–6</th>
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<tbody>
<tr>
<td>Muscle dysfunction</td>
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<td>Cachexia</td>
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<td>Anemia</td>
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<td>Muscle dysfunction</td>
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<td>Autonomic dysfunction</td>
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<td></td>
<td>anxiety/depression</td>
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<td>Systemic inflammation</td>
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<table>
<thead>
<tr>
<th>First Author</th>
<th>Journal</th>
<th>Type of Study</th>
<th>Patient Size (n)</th>
<th>Cardiac (%)</th>
<th>Hypertension (%)</th>
<th>Diabetes (%)</th>
<th>Psychiatric (%)</th>
<th>Cancer (%)</th>
<th>Osteoporosis (%)</th>
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<td>Observational</td>
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<td>Chest</td>
<td>Retrospective matched cohort</td>
<td>2699</td>
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<td>12.2</td>
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— signifies no data available.
Systemic inflammation is discussed in more details later in this article.

Hypoxia
Patients with COPD are subjected to hypoxia: either sustained hypoxia in patients with severe disease, or intermittent hypoxia during exercise or exacerbations. There are several effects of hypoxia that can influence atherogenesis, including systemic inflammation and oxidative stress, upregulation of cell-adhesion molecules, and hemodynamic stress.27–29 Animal studies have shown hypoxia to be a contributor to atherosclerosis in the presence of dyslipidemia, as increased lipid peroxidation, a marker of oxidative stress, and reduced levels of the antioxidant superoxide dismutase are found in the myocardial tissue of rats exposed to hypoxic environments.30,31

Hypoxia also induces hemodynamic stress, increasing the heart rate and cardiac index,32 and affects the renal circulation, reducing renal blood flow and activating the renin-angiotensin system, resulting in increased peripheral vasoconstriction and oxidative stress.33 Respiratory failure in patients with COPD is also associated with activation of the sympathetic nervous system,34 which is associated with an increased risk for cardiovascular disease.35

Polycythemia
Secondary polycythemia is a known complication of COPD, and occurs mainly as a result of chronic hypoxemia. A prospective study by Cote and colleagues,43 however, had shown that only 6% of their 683 COPD patients developed secondary polycythemia, perhaps because the development of polycythemia in COPD has been less common in recent times, and is thought to be due to more effective management of hypoxia in COPD such as the use of long-term oxygen therapy (LTOT) in patients who meet the criteria.

However, when present in COPD polycythemia can contribute to the development of pulmonary hypertension and pulmonary endothelial dysfunction with reduced cerebral and coronary blood flow, thus adding to the pathogenic cascade.44

Hypercapnic acidosis
Respiratory acidosis resulting from hypercapnia is a well-known occurrence in patients with COPD, particularly in the advanced phase. A recent study
by Minet and colleagues \cite{45} has shown that respiratory acidosis could be one of the potent mechanisms behind endothelial dysfunction, adding to the burden of cardiovascular complications.

**Abnormalities in vascular endothelial function/vessel wall**

Some \cite{46,47} but not all studies \cite{48} have demonstrated abnormal endothelial function in COPD patients in comparison with smokers who have not developed COPD.

Arterial stiffness can be assessed using carotid-femoral pulse-wave velocity (PWV), a measure that is predictive of cardiovascular events in healthy individuals and in patients with ischemic heart disease. \cite{49} Arterial stiffness is increased in COPD patients in comparison with healthy smokers \cite{50,51} and is associated with the FEV\(_1\) percent predicted emphysema and systemic inflammation, \cite{52} and may result from increased elastolysis in the vessel wall. \cite{53}

**Common Cardiovascular Complications**

HF is common in COPD patients, and COPD is common in HF patients. In a survey of COPD patients in primary care, 20% had previously unrecognized HF, \cite{54} which is associated with a worse prognosis in COPD patients. \cite{55}

A study of 186 consecutive patients with left ventricular systolic dysfunction in an HF clinic found that 39% had COPD diagnosed by spirometry, and those patients with HF and severe COPD had a worse prognosis than the HF patients with mild to moderate COPD or normal lung function. \cite{56} Higher mortality was again reported among patients with COPD when compared with individuals without lung disease in a study of 4132 patients hospitalized with cardiac failure in Norway. \cite{57}

In another prospective prognostic study performed as part of the EchoCardiography and Heart Outcome Study (ECHOS), 532 patients admitted with a clinical diagnosis of HF were studied. \cite{58} The prevalence of COPD in these patients was found to be 35% and was associated with a worse prognosis.

COPD is indeed a predictor of mortality in HF. \cite{30} Studies have shown 5-year survival in HF patients with COPD to be as low as 31%, compared with 71% in its absence. \cite{57} HF in COPD patients has often been postulated to be secondary to increased intrathoracic pressure–induced impaired low-pressure ventricular filling, as is expected with hyperinflated lungs in this population. \cite{59} However, Barr and colleagues \cite{60} have shown that computed tomography (CT)-quantified emphysema scores negatively correlated with ventricular filling even in a group without COPD and minor emphysema, in whom hyperinflation is unlikely to play a role. The investigators hypothesized that endothelial dysfunction associated with emphysema could contribute to impaired left ventricular filling and the consequent failure cascade.

Patients with COPD also have increased risk for cardiac arrhythmias. \cite{61} Following surgery for non-small cell lung carcinoma, patients with spirometric evidence of COPD had an increased risk for supraventricular tachycardia, and were found to be refractory to first-line treatment. \cite{62} Atrial fibrillation (AF) is also more common in COPD following coronary artery bypass grafting. \cite{63} In a study conducted in Finland on 738 patients with COPD, AF was found to be an independent predictor of increased mortality and poor health-related quality of life (HRQoL) in comparison with the general population. \cite{64}

Coronary artery disease is also common and is undertreated in patients with COPD. \cite{65} In a group of healthy Japanese men, CIMT (a measure strongly associated with atherosclerotic plaque burden) was significantly increased in individuals who smoked and had airflow limitation compared with matched smokers and nonsmokers. \cite{17} This finding suggests that smokers with a spirometric-based diagnosis of COPD may have evidence of subclinical atherosclerosis independent of cigarette smoking.

The presence of COPD in patients with myocardial infarction (MI) is also associated with a poorer prognosis. In a study of 14,703 patients with acute MI, all-cause mortality was 30% in patients with COPD versus 19% in those without COPD. \cite{66} Campo and colleagues \cite{14} assessed 11,118 consecutive patients with ST-elevation MI (STEMI) stratified according to the presence or absence of COPD. At the 3-year follow-up, COPD was found to be an independent predictor of mortality (hazard ratio [HR] 1.4, 95% confidence interval [CI] 1.2–1.6). Hospital readmissions from recurrent MI (10% vs 6.9%, \(P<.01\)) and HF (10% vs 6.9%, \(P<.01\)) were significantly more frequent in patients with COPD when compared with those without. Also hospital readmission for COPD was found to be a strong independent risk factor for recurrence of MI (HR 2.1, 95% CI 1.4–3.3) and HF (HR 5.8, 95% CI 4.6–7.5).

In a study of exacerbations of COPD from the United Kingdom Health Improvement Database, the incidence rate of MI was 1.1 per 100 patient-years, with a 2.27-fold increased risk of MI 1 to 5 days after exacerbation. \cite{67}

In another prospective study, 242 COPD patients admitted to hospital with an exacerbation were studied to observe the prevalence of MI
following hospitalization. Twenty-four patients (10%) were found to have elevated troponin, among whom 20 (8.3%; 95% CI 5.1%–12.5%) had chest pain and/or serial electrocardiographic changes, in keeping with MI. Overall, 1 in 12 patients met the criteria for MI.

**Interventions to Reduce Cardiovascular Complications**

**Smoking cessation**

A recent meta-analysis assessing the impact of smoking has shown a decline of acute coronary syndrome risk in 30 of 35 estimates with a 10% (95% CI 6–14, P<.001) pooled relative risk reduction, supporting the fact that smoking is an independent risk factor toward development of cardiovascular complications. Smoking cessation therefore unsurprisingly remains one of the primary cornerstones of cardiovascular risk management.

**Effective management of COPD**

It is well known that for every 10% decrease in FEV1, cardiovascular mortality increases by about 28%, and nonfatal coronary events increase by about 20% in mild to moderate COPD. Therefore, early detection and effective management of the disease is of importance in reducing the associated complications of this condition.

The use of current medications to treat COPD, however, has not been shown to be definitive toward reduction of cardiovascular events. Whereas observational studies have suggested that inhaled corticosteroids (ICS) may potentially confer benefit on cardiovascular events or mortality, randomized controlled trials (RCTs) have failed to show any significant effect of ICS therapy on MI or cardiovascular death. The use of long-acting inhaled β-agonists does not appear to produce an increased risk of cardiovascular deaths. The long-acting antimuscarinic, tiotropium, appears to confer an increased risk of cardiovascular death when used in a higher dose in the Respimat inhaler but not in the Handihaler formulation, which may even be associated with a decrease in cardiovascular mortality.

**Cardiovascular drugs**

Medications currently associated with cardiovascular risk reduction, such as β-blockers (BB), angiotensin-converting enzyme (ACE) inhibitors, statins, and angiotensin II receptor blockers (ARBs), have been shown in retrospective pharmacoepidemiologic studies to have an impact on the clinical outcome of COPD patients by reducing the cardiovascular events and mortality. These observational studies, however, suffer from immortal time bias, and prospective studies are required to definitively assess the benefits of these drugs in this population.

BB are known to improve survival of patients within a large spectrum of cardiovascular diseases, including ischemic heart disease and HF. In a large observational study involving 2230 COPD patients, the association of BB usage with all-cause mortality and risk of exacerbation was studied. Use of BB was found to be associated with a reduction in mortality as well as the risk of exacerbations in a broad spectrum of patients with COPD with concurrent cardiovascular disease. Importantly in a subgroup analyses, including patients with COPD but without overt cardiovascular disease, but with hypertension as the main remaining indication for the prescription of BB, similar outcomes were noted. This result further indicates the potential protective benefit of BB in COPD even in those with no known history of heart disease.

However, BB have been underprescribed in patients with COPD cardiovascular disease, largely because of the potential to worsen airflow limitation and consequent theoretical respiratory side effects (namely bronchospasm).

Another recent study also explored the association between BB therapy and outcomes in patients hospitalized with acute exacerbations of COPD with underlying ischemic heart disease, HF, or hypertension. The study accounted for the problem of immortal time bias, and found no improvement or worse mortality in COPD patients using BB. Judicious use of BB may therefore be warranted in patients with severe COPD and respiratory failure on LTOT in whom the use of BB was associated, in one study, with increased mortality.

Similarly, statins, ACE inhibitors, and ARBs are also widely used for the treatment and prevention of cardiovascular disease, and their potential role in other disease states has become increasingly recognized. Mortensen and colleagues studied the association of prior outpatient use of statins and ACE inhibitors on mortality for subjects of 65 years or older who were hospitalized with acute COPD exacerbations. A total of 11,212 subjects with a mean age of 74.0 years were studied in this group, of whom 32.0% were using ACE inhibitors or ARBs, the use of which was associated with significant reduction in 90-day mortality.
(odds ratio [OR] 0.55, 95% CI 0.46–0.66). A similar pharmacoepidemiologic study done by Mancini and colleagues75 suggested that statins in combination with either ACE inhibitors or ARBs improved cardiovascular and pulmonary outcomes not only in the high-risk but also in the low-risk COPD populations.

SKELETAL MUSCLE EFFECTS

A striking systemic consequence of COPD is the reduction in peripheral muscle mass, resulting in muscle wasting and dysfunction. Muscle dysfunction, with or without evidence of atrophy, can be defined physiologically as the failure to achieve the basic muscle functions of strength and resistance, the latter being inversely related to an increase in the fatigability of the muscle.

Reduced quadriceps strength in COPD is associated with reduced exercise capacity,87,88 compromised health status,89 increased need for health care resources,90 and mortality independent of airflow obstruction.91 Skeletal muscle weakness, particularly quadriceps weakness, has also recently been shown to be a feature of early disease,92 and its development is likely to be multifactorial with inflammation and oxidative stress93 being the predominant factors, coupled with physical inactivity.94,95 Several other factors such as protein synthesis/degradation imbalance and hypoxia have also been postulated to explain the initiation and the progression of muscle wasting in COPD patients.88,96

Prevalence

Eighteen percent to 36% of COPD patients present with net loss of muscle mass, which is responsible for weight loss in 17% to 35% of such patients.97 However, muscle wasting is also present in 6% to 21% of patients of normal weight.98 The reductions in mass and cross-sectional area of limb muscles of COPD patients have been linked to the impaired muscle strength seen in these patients. When limb-muscle strength is normalized per unit of mass or cross-sectional area, no differences can be observed between control subjects and COPD patients, suggesting that atrophy is indeed an important causative factor in the reduced limb-muscle strength and endurance in COPD.97 Hence, it could be argued that muscle wasting is a better predictor of HRQoL and survival than is body weight.99

Unintentional loss of muscle mass, unsurprisingly, has a significant impact on the quality of life, and can be associated with premature death.100

Fig. 2 illustrates the various pathophysiologic changes that are observed in skeletal muscles of COPD patients and the possible mechanisms implicated.

Pathophysiologic Changes Associated with Muscle Dysfunction/Wasting

Fiber redistribution results in an increase in the number of type IIX muscle fibers,101,102 which, in turn, is associated with significant muscle atrophy.102 Alterations in muscle bioenergetics in skeletal limb muscle of COPD patients correlate with exercise tolerance. For example, the early lactate release that occurs during exercise, the increased phosphate/phosphocreatine relationship during submaximal exercise, and the reduced activity of oxidative enzymes in these patients all indicate a change in muscle bioenergetics.103

Altered capillary structuration has also been found in the skeletal muscle of COPD patients. Electron and optic microscopy studies show reduced capillary density and the number of contacts between capillaries and fibers in skeletal muscles of COPD patients.104

Factors Contributing to Muscle Dysfunction

Several factors, such as protein synthesis/degradation imbalance, hypoxia, inactivity, inflammation, and oxidative stress, have been proposed to explain the initiation and the progression of muscle wasting in COPD.96,97 Mitochondrial dysfunction, apoptosis, and oxidative stress have all also been implicated to the wasting and dysfunction observed in COPD.

Mitochondrial dysfunction is manifested as reduced citrate synthase activity that correlates with time to fatigue of the muscle,105 while reduced mitochondrial oxidative phosphorylation and coupling have been associated with reduced muscle mass and endurance.106

Other factors that contribute to this muscle dysfunction include the following.

- Abnormal protein metabolism. A substantial proportion of COPD patients is characterized by low fat-free mass with altered muscle and plasma amino acid levels, suggesting abnormal protein metabolism.107 The signaling pathways that govern muscle hypertrophy and/or atrophy have yet to be fully defined. However, several key factors have been identified. Fig. 3 summarizes the salient pathways governing skeletal muscle metabolism. Marked activation of the ubiquitin-proteasome pathway is found in muscle of patients with COPD, and is thought to be one of the key factors in muscle atrophy and dysfunction as seen in COPD patients.108,109
Poor nutritional intake and unmatched calorie expenditure are further factors contributing to muscle wasting in COPD patients. Chronic usage of oral corticosteroids is also a well-known contributor to myopathy in this group. Previous studies have shown that the histology of steroid-induced myopathy in patients with COPD is of global myopathy affecting both type IIa and IIb fibers, and type I fibers to a lesser extent. However, administration of corticosteroids for relatively short periods of time, for example during an exacerbation, has not been shown to cause any significant deleterious effect on the skeletal muscle of COPD patients.

Hypoxia is implicated in mitochondrial biogenesis, oxidative stress, inflammation, and autophagy. It results in enhanced cytokine production by macrophages, contributing to the activation of the tumor necrosis factor (TNF) system. Significant inverse correlations between partial pressure of arterial oxygen and circulating TNF-α and soluble TNF-receptor levels have been reported in patients with COPD, limiting the production of energy and possibly affecting the protein synthesis also.

Hypercapnic acidosis can inhibit the oxidative enzymes, further contributing to protein degradation and the process of muscle wasting.

Inflammation, as in cardiovascular complications, is another mechanism contributing to skeletal muscle dysfunction in COPD patients. Relatively fewer data are currently available on the concentration of cytokines in muscle of COPD patients, the most studied being TNF-α. High levels of TNF-α protein in serum have been associated with quadriceps weakness, and COPD patients with low fat-free mass (FFM) are reported to show high mRNA levels of TNF-α in the quadriceps, together with lower body mass index (BMI). Of interest, high levels of C-reactive protein (CRP) have been found to be inversely related to the distance covered in a 6-minute walking test in COPD patients.

**Fig. 2.** The common manifestations and underlying pathophysiologic changes of skeletal muscle dysfunction in COPD patients.
suggesting a role for chronic inflammation in these patients.\textsuperscript{118}

**Interventions to Improve Skeletal Muscle Dysfunction**

- Exercise training is the single most important therapeutic intervention to treat muscle dysfunction/wasting in patients with COPD.\textsuperscript{119} Improving exercise tolerance by enhancing muscle strength, with consequent improved endurance and reduced fatigue, have all proved to be very effective.\textsuperscript{119} Exercise training improves body weight by improving FFM, enhancing oxygen delivery to the muscle mitochondria and fiber-type redistribution.\textsuperscript{119,120}
- Oxygen therapy and consequent correction of hypoxia in suitable candidates have also been shown to improve the mitochondrial oxidative capacity in COPD patients.\textsuperscript{120,121}
- Smoking cessation is likely to be an important aspect in improving muscle dysfunction. Chronic smoking has been associated with diverse mitochondrial respiratory chain (MRC) dysfunction in lymphocytes. In a study of MRC function in peripheral lymphocytes of 10 healthy chronic smokers before and after cessation of smoking,\textsuperscript{122} smokers showed a significant decrease in complex IV MRC activity and respiration compared with control lymphocytes, which returned to normal values after cessation of tobacco smoking.
- Other novel therapies such as the antioxidant N-acetylcysteine\textsuperscript{123} and peroxisome proliferator-activated receptors (such as polyunsaturated fatty acids)\textsuperscript{120,124} are potential interventions that may improve muscle insufficiency in COPD patients, and are currently in the process of being tried and tested.

**OSTEOPOROSIS**

Osteoporosis is a systemic skeletal disorder characterized by low bone mineral density (BMD) and microarchitectural changes, leading to impaired bone strength and increased risk of fracture.\textsuperscript{4}

Low BMI, advanced age, female sex, chronic use of oral corticosteroids, and endocrinologic disorders such as hyperthyroidism and primary hyperparathyroidism have all been implicated as risk factors in the development of osteoporosis in
the general population. Predictably, osteoporosis is a well-recognized comorbidity of COPD patients and is an important area of consideration for therapeutic interventions.

The most commonly used tool to measure BMD is dual-energy x-ray absorptiometry (DEXA), which is used to define osteoporosis and provides a useful estimate of fracture risk. The T score is one of the principal parameters used to measure BMD, and is calculated by subtracting the mean BMD of a young-adult reference population from the patient’s BMD and dividing it by the standard deviation of the reference population. According to the World Health Organization (WHO), a T score greater than −1 is accepted as normal, T scores between −1 and −2.5 are classified as osteopenia, and T scores of less than −2.5 are defined as osteoporosis.

Prevalence of Osteoporosis in COPD

The prevalence of osteoporosis in COPD varies between 4% and 59%, depending on the diagnostic methods used and the severity of the COPD population.

A recent systematic review calculated an overall mean prevalence of osteoporosis of 35% from 14 articles by measuring BMD in a COPD population. The individuals in these studies had a mean age of 63 and a mean FEV$_1$ percent predicted of 47%.

More than half of the patients with COPD recruited for the large TORCH (Toward a Revolution in COPD Health) trial (6000 patients) had osteoporosis or osteopenia as determined by DEXA scan.

In another cross-sectional study, the prevalence of osteoporosis was 75% in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV disease, and strongly correlated with reduced FFM. Another important finding in this study was that the prevalence rate was high even for males, with an even higher incidence in postmenopausal women.

Another large cohort of 1634 COPD subjects was studied longitudinally with 259 smoker and 186 nonsmoker controls in a study evaluating CT bone attenuation of the thoracic and lumb vertebrae, the extent of emphysema and coronary artery calcification on CT scans, and clinical parameters and outcomes. Bone attenuation was lower in the COPD patients than in control subjects, and correlated positively with FEV$_1$ (P = .014), FEV$_1$/forced vital capacity ratio (P<.001), FFM index (P<.001), and CRP (P<.001), and negatively with the extent of emphysema (P<.001). Lower CT bone attenuation was also found to be associated with higher exacerbation (P = .022) and hospitalization rates (P = .002).

In a Norwegian cross-sectional study of 1004 consecutively admitted COPD patients attending a 4-week rehabilitation program, the prevalence of vertebral deformities was found to be significantly higher in COPD patients than in the control group (P<.0001). An increase in severity of airflow limitation from GOLD stage II to stage III was associated with an almost 2-fold increase in the average number of vertebral deformities. Of note, significant differences between COPD patients and controls were also found for pack-years (P<.0001), and use of calcium/vitamin D (P<.0001) and oral corticosteroids (P<.0001).

Potential Contributors to Osteoporosis in COPD

Corticosteroids

Oral glucocorticosteroids (OGCS) have both direct adverse effects on bone and indirect effects attributable to muscle weakening and atrophy. OGCS are known to cause a decrease in vascular endothelial growth factor, skeletal angiogenesis, bone hydration, and strength. These effects are both dose-dependent and duration-dependent. Fewer adverse effects are seen in episodic usage of OGCS in comparison with continuous use, but lower continuous doses have fewer detrimental effects on bone than frequent high-dose therapy, because systemic usage of corticosteroids can cause rapid bone loss within the first few months of treatment, followed by a slower 2% to 5% loss per year with chronic use. However, ICS have not been shown to aggravate the bone mineral loss in COPD patients.

Inflammation

Studies suggest that COPD and associated systemic inflammation is a risk factor for osteoporosis independent of other potentiators such as age and oral corticosteroid therapy. In a Chinese study, the presence of systemic inflammation was associated with a greater likelihood of low BMD, and multivariate logistic regression analysis showed that TNF-α and IL-6 were independent predictors of low BMD. Both these factors are known to stimulate osteoclasts and increase bone resorption through receptor activator of nuclear factor (NF)α-B ligand (RANKL)-mediated bone resorption in vitro. In addition, many other cytokines have been found to interact with the osteoprotegerin/RANKL system, supporting the concept that inflammatory mediators possibly contribute to the regulation of bone remodeling in COPD patients.

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**Calcification paradox**

Mounting data support a calcification paradox, whereby reduced BMD is associated with increased vascular calcification. Furthermore, BMD is more prevalent in older persons with lower BMI. Therefore, although BMI and coronary artery calcification (CAC) exhibit a positive relationship in younger persons, it is predicted that in older persons and/or those at risk for osteoporosis, an inverse relationship between BMI and CAC may apply. Kovacic and colleagues studied 9993 subjects who underwent percutaneous coronary intervention. Index lesion calcification (ILC) was analyzed with respect to BMI. In multivariable modeling, BMI was an independent inverse predictor of moderate to severe ILC (OR 0.967, 95% CI 0.953–0.980; \( P < .0001 \)).

**Therapeutic Interventions**

Prevention and treatment of osteoporosis involves both pharmacologic and nonpharmacologic interventions.

**Nonpharmacologic measures**

Nonpharmacologic interventions include simple measures such as smoking cessation, and alcohol consumption in moderation along with good nutrition. As discussed earlier, exercise training, particularly weight-bearing and strengthening exercise performed at least 3 times per week, may be effective for maintaining skeletal health, given the association of reduced physical activity with bone loss and fracture in elderly COPD patients. Pharmacologic measures

COPD patients, with or without diagnosed osteoporosis, should be encouraged to take calcium (1000 mg/d) and vitamin D (800 IU/d) supplements routinely, as these have been shown to reduce the risk of fracture in this cohort. Definitive therapy is recommended in documented fragility hip or vertebral (clinical or morphometric) fracture; or T score lower than –2.5; or with less marked bone loss (T score between –1 and –2.5) and 1 major criterion (use of systemic corticosteroids [3 months/year], major fragility fracture [spine-hip] and so forth). An oral bisphosphonate, such as alendronate and risedronate, is currently considered as the first line of treatment of osteoporosis together with vitamin D and calcium supplementation. Bisphosphonates act by inhibiting bone resorption, and have also been shown to prevent osteoblast and osteocyte apoptosis.

Anabolic drugs such as the human parathyroid hormone (PTH) analogue teriparatide (PTH1–34) are also being increasingly used to treat osteoporosis in COPD patients, particularly in postmenopausal women and men with advanced osteoporosis. These agents act by stimulating bone formation through effects on osteoblasts and osteocytes, and therefore have great relevance predominantly in OGGS-induced osteoporosis.

Efforts should be made to detect and treat low BMD in COPD patients to minimize fracture risk. Bone densitometry is widely available and should be used to screen patients at risk of low BMD, particularly those with low BMI, as current rates of detection and treatment of osteoporosis are low. Lehouck and colleagues have suggested a more aggressive approach to the diagnosis and management of low BMD in COPD, and this should be widely implemented to minimize the risk of osteoporotic complications. In this context the term FRAX has been described. FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that offers models for assessment of fracture likelihood in both men and women from the evidence provided from clinical risk factors such as age, sex, BMI, prior fragility fracture, smoking status, ethanol abuse, and prior use of corticosteroids. With FRAX, the 10-year fracture probability can be derived using these clinical risk factors, alone or in conjunction with femoral neck BMD, to enhance fracture-risk prediction and to differentiate the patients who will benefit most from definitive treatment. It is hoped that FRAX will become an increasingly used tool in the future, but for the moment the identification of patients who need antiresorptive treatment remains based on clinical history, BMD, and prevalent fracture status.

**NUTRITIONAL EFFECTS IN COPD**

Nutritional abnormalities are also a common problem in COPD patients. There are 3 types of nutritional abnormality that occur in this population: semistarvation (low BMI with normal or above-normal FFM index), muscle atrophy (normal or above-normal BMI with low FFM index), and cachexia (low BMI with low FFM index). Prevalence and Implications

Weight loss has been reported in about 50% of patients with severe COPD and, although less common, it is still observed in about 10% to 15% of mild to moderate COPD. Several studies have shown an association between malnutrition and impaired pulmonary status in patients with COPD. Poor nutritional status and consequent weight loss in these patients is known to be associated increased gas trapping, lower diffusing capacity, and lower exercise
tolerance compared with their normal nourished counterparts. Impairment of skeletal muscle function along with reduction in diaphragmatic mass, with a decrease in strength and endurance of the respiratory muscle that could occur in a malnourished state, have all been implicated in causing these adverse effects on pulmonary function.

Loss of skeletal muscle bulk is the main contributor to weight loss in COPD, with loss of fat mass contributing to a lesser extent. It is important to recognize that if nutritional assessment includes only body weight and unintentional weight loss, some patients with normal BMI would go undetected despite being depleted of FFM. In a cross-sectional study involving 300 COPD patients requiring LTOT, 17% of patients had a low BMI, whereas the prevalence of FFM depletion was 2 times higher (around 38%).

This finding is of therapeutic importance, as improving the nutrition in COPD patients can lead to improvement in anthropometric measures and muscle strength, thus resulting in improved and better quality of life and survival rates in these patients. Post hoc analysis of COPD patients who gain weight has suggested a decrease in mortality. At least one study has reported improved immune function as a result of nutritional support.

**Factors Contributing to Nutritional Depletion**

The cause of nutritional abnormalities in COPD patients seems to be multifactorial, as with other systemic effects. Box 2 lists the important contributory mechanisms.

**Therapeutic Interventions**

Dietary intervention following a proper nutritional assessment remains one of the primary cornerstones in the management of this condition.

A meta-analysis of 13 RCTs on the effects of nutritional support in stable COPD patients showed significant improvements in favor of nutritional support for body weight \( P < .001 \) (in 11 studies) and grip strength \( P < .050 \) (in 4 studies) associated with greater increases in mean total protein and energy intakes following the intervention.

Similar results have been produced by Ferreira and colleagues, who assessed 17 RCTs from the Cochrane Airways Review Group Trials Register. The meta-analysis showed that nutritional supplementation produced significant weight gain in patients with COPD, especially in those who were malnourished. In the 11 RCTs that studied 325 undernourished patients, there was a mean difference of 1.65 kg (95% CI 0.14–3.16) in favor of supplementation. Nourished patients, however, may not respond to supplemental feeding to the same degree as their undernourished counterparts (1 RCT with 71 participants: standardized mean difference [SMD] of 0.27, 95% CI −0.20–0.73).

Ferreira and colleagues found a significant change from baseline in FFM index (overall SMD 0.57, 95% CI 0.04–1.09), which became even more significant in undernourished patients (3 RCTs, 125 participants: SMD 1.08, 95% CI 0.70–1.47). This study also emphasized the significant improvement in respiratory muscle strength and HRQoL that occurs in undernourished patients following a nutritional intervention.

This nutritional intervention can be in the form of oral supplementation, enteral nutrition, or, in some extreme cases, parenteral nutrition. A diet rich in protein and fat content is desirable, as an increase in fat calories with a decrease in carbohydrate calories helps to limit the amount of carbon dioxide production while still maintaining an adequate intake of protein for lean muscle mass. In addition, the diet of these patients should include a good supply of vitamins, minerals, and antioxidants. In this context, \( \omega-3 \) fatty acid has been shown to be of some value in combating the anti-inflammatory properties of TNF-\( \alpha \). Therefore, this could potentially be of novel therapeutic benefit in achieving good nutritional status in these patients.

**OBESITY AND OBSTRUCTIVE SLEEP APNEA IN COPD**

The prevalence of obesity, defined as BMI greater than 30 kg/m\(^2\), has multiplied during the last decades, and varies from 10% to 20% in most European countries to 32% in the United States. It plays a major role in the development of the metabolic syndrome, and has been identified as an
important risk factor for chronic diseases such as type 2 diabetes mellitus and cardiovascular disease. A link between obesity and COPD is also being increasingly recognized. The risk of developing obesity is increased in patients with COPD as a result of physical inactivity in daily life in these patients in comparison with healthy age-matched controls. In addition, patients with COPD who receive repeated courses of systemic GCs are at increased risk of truncal obesity as a result of steroid-mediated redistribution of stored energy and the stimulatory effect on intake.

As discussed previously, low BMI is associated with increased all-cause and COPD-related mortality, unrelated to disease severity. By contrast, the relative risk for mortality seems somewhat decreased in overweight and obese patients with COPD, particularly in GOLD stage 3 to 4, imparting a sort of protective effect, the so-called obesity paradox, as mortality is increased in those with disease of GOLD stage 1 to 2 with obesity traits.

Chronic low-grade inflammation is also a hallmark of obesity, insulin resistance, and type 2 diabetes. Besides the presence of chronic airflow obstruction, low-grade systemic inflammation could therefore be one of the common mechanisms that may be responsible for the observed mortality and morbidity in obese COPD patients.

In this context, mention should also be made of obstructive sleep apnea (OSA). OSA syndrome (ie, OSA and excessive daytime sleepiness) affects at least 4% to 5% of middle-aged persons. Well-recognized risk factors include excess body weight, nasal congestion, alcohol, smoking, and menopause in women.

Epidemiologic studies have shown that 20% of patients with OSA also have COPD, whereas 10% of patients with COPD have OSA independent of disease severity. Such bidirectional interplay between OSA and COPD has been given the term overlap syndrome. Possible shared mechanistic links include increased parasympathetic tone, hypoxemia-related reflex bronchoconstriction/vasoconstriction, irritation of upper airway neural receptors, altered nocturnal neurohormonal secretion, proinflammatory mediators, within-breath and interbreath interactions between upper and lower airways, and lung volume–airway dependence.

**Management of OSA and COPD**

It is currently unclear whether long-term positive airway pressure therapy for COPD patients without OSA affects outcomes. In one such study, 122 COPD patients hospitalized with respiratory failure were randomized to LTOT versus noninvasive nocturnal ventilation (positive airway pressure) plus oxygen therapy. There was an improvement in HRQoL and reduction in length of stay in the intensive care unit in the noninvasive ventilation group, but no difference in mortality or subsequent hospitalizations was found.

Thus the overlap syndrome represents a condition with important phenotypic characterization, and clarifies the frequent association, symptomatic load, and mortality consequences noted. However, the use of positive airway pressure in overlap syndrome needs further assessment.

**ANEMIA IN COPD**

As discussed earlier, in severe COPD, polycythemia with a raised hematocrit is known to be a common phenomenon. However, just as for other chronic conditions, COPD could also be associated with anemia.

The WHO defines anemia as a disease associated with low hemoglobin (males <13.0 g/dL and females <12 g/dL).

### Prevalence

Key findings of studies of anemia in COPD are summarized in Table 3.

A study by Rutten and colleagues in the Netherlands involved 321 patients with COPD admitted for pulmonary rehabilitation, and found anemia in 20% of the patients and polycythemia in another 8%. There was no difference in disease-related outcomes or other comorbidities in the patients with and without anemia. However, after adjustment for confounders, anemia was found to be an independent determinant for higher CRP levels and lower BMD.

Low blood count can also be defined by hematocrit (<39% in men and <36% in women). In a French study involving severe COPD patients who required LTOT, a reduced hematocrit level was associated with increased mortality, whereas a raised hematocrit level was protective, independent of other markers of mortality.

### Pathogenesis

The anemia of chronic illness is typically a normocytic anemia and is most commonly observed in patients with infectious disease, and inflammatory or neoplastic diseases.

COPD fulfills the criteria of a chronic, inflammatory, multisystem disease that would be expected to result in anemia. John and colleagues studied 101 COPD patients and determined the
### Table 3
PubMed search: anemia/anemia AND COPD OR chronic obstructive pulmonary disease in title/abstract

<table>
<thead>
<tr>
<th>Authors, Ref. Year</th>
<th>Journal</th>
<th>Study Type</th>
<th>Prevalence (%)</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>John et al, 2005</td>
<td>Chest</td>
<td>Prospective (N = 101)</td>
<td>13/101 = 13</td>
<td>No outcome data</td>
<td>EPO resistance?</td>
</tr>
<tr>
<td>John et al, 2006</td>
<td>Int J Cardiol</td>
<td>Retrospective hospital records (N = 312)</td>
<td>23</td>
<td>No outcome data</td>
<td>COPD hospitalized</td>
</tr>
<tr>
<td>Cote et al, 2007</td>
<td>Eur Respir J</td>
<td>Prospective cohort (N = 677)</td>
<td>116/677 = 17</td>
<td>Independent predictor dyspnea</td>
<td>COPD outpatients</td>
</tr>
<tr>
<td>Chambellan et al, 2005</td>
<td>Chest</td>
<td>Retrospective database (N = 2524)</td>
<td>M: 12.6, F: 8.2</td>
<td>Hb as outcome predictor</td>
<td>LTOT</td>
</tr>
<tr>
<td>Krishnan et al, 2006</td>
<td>BMC Pulm Med</td>
<td>Post hoc analysis from general population (N = 495)</td>
<td>7.5</td>
<td>Anemia associated with worse HRQoL</td>
<td>No outcome</td>
</tr>
<tr>
<td>Schonhofer et al, 1998</td>
<td>Crit Care Med</td>
<td>Prospective 20 anemic adults (10 COPD)</td>
<td>—</td>
<td>Correction of Hb improves breathing pattern and efficacy</td>
<td>No outcome</td>
</tr>
<tr>
<td>Kollert et al, 2011</td>
<td>IJCP</td>
<td>Retrospective hospital record database (N = 326)</td>
<td>14.7</td>
<td>Determinants of anemia: pH, PaO₂</td>
<td>No outcome</td>
</tr>
<tr>
<td>Boutou et al, 2011</td>
<td>Respiration</td>
<td>Prospective, 283 stable COPD</td>
<td>10</td>
<td>Association with dyspnea and exercise capacity</td>
<td>Good patient selection</td>
</tr>
<tr>
<td>Rasmussen et al, 2010</td>
<td>Clin Epidemiol</td>
<td>Retrospective hospital records (N = 222)</td>
<td>42/222 = 18</td>
<td>Increased mortality at 90 d</td>
<td>Mechanically ventilated</td>
</tr>
<tr>
<td>Markoulaki et al, 2011</td>
<td>Eur J Intern Med</td>
<td>Prospective observational 93 acute exacerbated COPD</td>
<td>NA</td>
<td>Hb decreased, EPO increased</td>
<td>No outcome</td>
</tr>
</tbody>
</table>

**Abbreviations:** EPO, erythropoietin; Hb, hemoglobin; HRQoL, health-related quality of life; LTOT, long-term oxygen therapy; NA, no data available; PaO₂, partial pressure of oxygen in arterial blood.
prevalence of anemia and its relationship to body mass and weight loss, inflammatory parameters, and erythropoietin levels. Anemia was diagnosed in 13 patients (12.8%). These patients showed elevated erythropoietin levels and had increased systemic inflammation markers (raised CRP) in comparison with the nonanemic patients. This finding raises the possibility that erythropoietin resistance, as is possible in the COPD cohort, is potentially mediated by chronic inflammation.

**Management**

As for any other anemia of chronic disease, treatment of the underlying disease is the therapeutic approach of choice for anemia in COPD.\(^{178}\)

The level of hemoglobin is strongly and independently associated with increased functional dyspnea and poorer exercise tolerance, and is therefore an important contributor to poor quality of life.\(^{43}\) Schönhofer and colleagues\(^{179}\) demonstrated that correction of anemia with blood transfusions (among 20 patients with severe COPD) significantly reduced disease-related elevations in minute ventilation and work of breathing, suggesting that anemia correction may be beneficial in alleviating dyspnea and improving exercise capacity. Therefore, blood transfusion in selected cases may be necessary, as erythropoietin is unlikely to work in this cohort because of end-organ resistance. Iron supplements, likewise, are unlikely to be useful and possibly could have a deleterious effect by adding to the burden of systemic oxidative stress.\(^{6}\)

**Autonomic Dysfunction**

The autonomic nervous system (ANS) controls physiologic processes such as regulation of the airway smooth muscle tone, fluid transport through the airway epithelium, capillary permeability, bronchial circulation, and release of mediators from inflammatory cells.\(^{180}\) Autonomic dysfunction (AD) is a known phenomenon in COPD patients,\(^{181}\) and may be an important factor in the pathogenesis of the disease because of the multiple parameters that are under control of the ANS such as the arterial and cardiac baroreceptors,\(^{182}\) the bronchopulmonary C fibers, and pulmonary stretch receptors, which are capable of triggering ventilation, bronchomotor, and cardiovascular effects.\(^{183,184}\)

Recurrent hypoxemia, hypercapnea, increased intrathoracic pressure swings resulting from airway obstruction, increased respiratory effort, and systemic inflammation along with the use of \(\beta\)-sympathomimetics have all been implicated as trigger factors for AD as observed in COPD.\(^{181}\)

**Prevalence and Clinical Implications**

Tug and colleagues\(^{185}\) assessed the prevalence of AD according to disease severity in 35 stable COPD patients. Sympathetic system (SS) was evaluated with sympathetic skin response (SSR), and QT- and QTc-interval (milliseconds) analyses. The parasympathetic system was evaluated with the variations in heart-rate interval. AD was detected in 20 patients (57%), parasympathetic dysfunction (PD) in 14 (40%), mixed-type dysfunction in 5 (14%), and sympathetic dysfunction (SD) in only 1 patient (3%). For the 12 patients with mild COPD, there were cases of isolated SD in 1 patient (8.5%), isolated PD in 5 (42%), and AD in 6 (50%). For the 23 moderate to severe COPD patients, mixed AD was detected in 5 patients (22%), isolated PD in 9 (39%), and AD in 14 (61%).

This imbalance in the autonomic nervous activity can contribute to airway narrowing via an effect on the airway smooth muscle, bronchial vessels, and mucous glands in the bronchial wall, and therefore could add to disease progression and severity.

Correction of hypoxia and control of the systemic inflammation seem reasonable target strategies that may help to improve health status in COPD patients.

**LUNG CANCER AND COPD**

With a shared common environmental risk factor in exposure to cigarette smoke, it is understandable why lung cancer is one of the most frequent comorbidities and one of the commonest causes of death in COPD patients.

**Prevalence**

Previous studies have shown that COPD is an independent risk factor for the development of lung cancer and that having moderate to severe COPD can increase the risk of developing lung cancer up to almost 5-fold.\(^{186,187}\)

Thirty-eight percent of deaths in individuals with mild to moderate airflow limitation in the Lung Health Study died of lung cancer.\(^{10}\) In addition to these 57 deaths, another 35 participants were diagnosed with the disease but survived to the end of follow-up.

An inverse correlation between the degree of airflow obstruction and the risk for lung cancer was demonstrated in an analysis of 22-year follow-up data of 5402 participants from the first National Health and Nutrition Examination Survey (NHANES I), including a total of 113 cases of lung cancer.\(^{186}\) Tockman and colleagues\(^{189}\) and
Skillrud and colleagues have previously demonstrated that the incidence of lung cancer increased in individuals with COPD as their FEV₁ declined, a relationship that withstood correction for lifetime cigarette smoke dosage.

Fig. 4 summarizes the inverse relationship observed between lung cancer and lung function values as seen in COPD patients. Unsurprisingly, lung cancer along with cardiovascular diseases comprises two-thirds of all deaths in COPD patients.

Recent studies also indicate that emphysema and airflow limitation are risk factors for lung cancer, independent of exposure to cigarette smoke. Cross-sectional studies have shown that after allowing for cigarette-smoke exposure, reduced FEV₁ (as seen in COPD) is the single most important risk factor for lung cancer, and that these 2 diseases are linked by more than smoking exposure alone.

An Italian study has also shown that airflow limitation is primarily a risk factor for squamous cell lung cancer (95% CI 1.63–18.5; \( P = .006 \)), whereas symptoms of chronic bronchitis without COPD is a risk factor (risk greater than 4-fold) for adenocarcinoma of the lung. In a subset analysis, the association of concurrent bronchitic symptoms and COPD imparted a 3-fold increased risk for squamous cell carcinoma of the lung, further consolidating the link between these 2 conditions.

Pathogenesis and Clinical Implications of Lung Cancer in COPD

The pathogenic mechanism linking these conditions remains unclear, although like other comorbidities in COPD it seems to be multifactorial.

Inflammation and oxidative stress seem to play important roles. The process of epithelial-to-mesenchymal transition (EMT), in which cells undergo a switch from an epithelial phenotype to a mesenchymal phenotype, is an important phenomenon that occurs in both patients with lung cancer and COPD patients.

Studies have also shown that inflammation directly promotes EMT by inducing the expression of E-cadherin transcriptional repressors, which could explain the connecting link between these 2 conditions. An exaggerated inflammatory response, leading to aberrant airway epithelial and matrix remodeling characterized by excessive growth factor release and elevated matrix metalloproteinases (MMP), has also been postulated as a possible mechanism connecting the 2 conditions.

NF-κB activation has also been suggested as a link between inflammation and lung cancer. Synergistic effects of latent infection and cigarette smoking cause chronic airway inflammation through enhanced expression of cytokines and adhesion molecules, possibly through NF-κB–mediated activation. Some of the cytokines can also inhibit apoptosis, interfering with cellular repair and promoting angiogenesis.

Retrospective studies have also suggested that reducing pulmonary inflammation with ICS or systemic inflammation with statin therapy may reduce the risk of lung cancer in COPD patients, adding further support for a role for inflammation as a common link in both of these conditions.

Studies have also suggested specific candidate gene loci as potential genetic links connecting lung cancer and COPD. The genes identified in these studies suggest that this common genetic susceptibility may be mediated through receptors expressed on the bronchial epithelium that implicate common molecular pathways underlying both COPD and lung cancer.

The transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates multiple antioxidant and detoxifying genes, has been shown to be downregulated in COPD lungs and may contribute to the increased susceptibility of COPD patients to lung cancer, because Nr2 plays an important role in defense against carcinogens in tobacco smoke by regulating the expression of several detoxifying enzymes. Epidermal growth factor receptor (EGFR), which promotes epithelial proliferation, also has increased expression in the lungs of COPD patients, which could promote carcinogenesis.

As the increased risk of lung cancer in COPD may be a reflection of increased inflammation and oxidative stress in the lungs, anti-inflammatory
therapies or antioxidants should hypothetically diminish the risk of lung cancer.

**PSYCHOLOGICAL EFFECTS IN COPD**

Anxiety and depression are common in patients with COPD, and have an impact on the psychosocial aspects of the management of this disease. Prognostic studies involving patients with COPD have mostly focused on physiologic variables, with less attention given to the psychological aspects of the disease.

**Prevalence**

The prevalence of generalized anxiety disorder in COPD patients ranges between 10% and 33%, and that of panic attacks or panic disorder between 8% and 67%. Disease severity in COPD has not clearly been associated with the magnitude of anxiety/depression.

Estimates of the prevalence of depression and depressive symptoms vary in COPD patients, ranging from 6% to 60%. Hanania and colleagues studied the prevalence and determinants of depression in COPD patient in the ECLIPSE study. The study cohort consisted of 2118 subjects with COPD, 335 smokers without COPD (smokers), and 243 nonsmokers without COPD (nonsmokers). A total of 26%, 12%, and 7% of COPD, smokers, and nonsmokers, respectively, suffered from depression. Using a multivariate logistic regression model, increased fatigue, higher score for St George’s Respiratory Questionnaire for COPD patients, younger age, female sex, history of cardiovascular disease, and current smoking status were all significantly associated with depression in this cohort.

**Clinical Implications**

Depression in COPD might result from a vicious cycle of sedentary lifestyle, smoking habits, and poor nutritional and health status. There is increasing evidence that inflammation itself could be a mediator of depression in COPD patients. Depressive symptoms were found to be strong predictors of mortality (OR 1.9, 3.6, and 2.7, respectively), independent of other markers of disease severity and risk factors, in COPD patients in 3 studies whereas one other study found no association between mortality and depression after adjustment for disease severity.

Therefore, the effect of depression on function in COPD patients and the early recognition and treatment of symptoms remain inherent important aspects in the management of this cohort.

**DIABETES AND METABOLIC SYNDROME IN COPD**

**Prevalence and Pathogenesis**

Studies have shown prevalence rates for diabetes of between 1% and 16% in patients with COPD. Large population studies have also shown that there is an increased prevalence of diabetes among COPD patients (risk ratio [RR] 1.5–1.8), even in patients with mild disease.

Poulain and colleagues looked at a cohort of 28 male patients with COPD, and divided patients according to their body habitus. The study showed that presence of obesity, particularly abdominal obesity, was associated with metabolic and inflammatory abnormalities that are typically associated with the development of cardiovascular diseases and diabetes, such as increased levels of insulin, TNF-α, and IL-6, and may mediate insulin resistance by blocking signaling through the insulin receptor. This finding further cements the common inflammatory pathway theory in the pathogenesis of the systemic effects of COPD.

Rana and colleagues also performed a prospective cohort study in which they looked at the relationship of COPD and asthma with the development of type 2 diabetes. During 8 years of follow-up, a total of 2959 new cases of type 2 diabetes were documented. The risk was significantly higher for patients with COPD than for those without (multivariate RR 1.8, 95% CI 1.1–2.8), but this was not the case among the asthmatics. This finding would further corroborate the fact that COPD is potentially a risk factor for the development of diabetes.

**Management and Clinical Implications**

Hyperglycemia, especially during acute exacerbations of COPD, is associated with poorer outcomes of acute noninvasive ventilation, longer inpatient stay, and higher rates of in-hospital mortality. Therefore, it is important to identify underlying hyperglycemic status in COPD patients to reduce the burden of morbidity and mortality as well as unnecessary utilization of health care resources.

The metabolic syndrome is a complex disorder and an emerging clinical challenge, recognized clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidemia, elevated blood pressure, and high blood glucose and/or insulin resistance. It is also associated with a prothrombotic state and a proinflammatory state. Patients with COPD often have 1 or more components of the metabolic syndrome, which are, at least in part, independent of treatment with steroids and/or physical inactivity.
Clini and colleagues also postulated that the metabolic syndrome was more likely to be present in COPD patients, as augmented levels of circulating proinflammatory proteins from both the lung and adipose tissue (adipokines) overlap in these patients. This coexistence perhaps rests on several factors including the presence of physical inactivity, systemic inflammation partly related to smoking habit, sedentary lifestyle, airway inflammation, adipose tissue, and inflammatory marker activation, among others.

Apart from the risks per se from high glucose level already described, COPD patients with hyperglycemia are likely to have more than one species of bacteria grown from sputum, suggesting impaired immunity. Although some nondiabetic COPD patients have hyperglycemia induced by systemic corticosteroids during exacerbations, this is more likely in the context of diabetes, therefore oral hypoglycemic medications or insulin may be a necessity.

Preventive measures include lifestyle advice including dietary guidance, and regular screening of those at higher risk, given the higher prevalence and adverse clinical impact of diabetes on COPD patients. This approach would potentially enable earlier diagnosis and prevention of complications.

There should also be more focus on global interventions intended at altering factors such as physical deconditioning and obesity, as such an approach may help slow the metabolic complications seen in COPD patients, particularly those with features of the metabolic syndrome.

### SYSTEMIC INFLAMMATION IN COPD

As described earlier, systemic inflammation is a well-established occurrence in COPD patients.

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**Table 4**

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Actions</th>
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<tbody>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
</tr>
<tr>
<td>Interleukin (IL)-6</td>
<td>Cardiovascular and skeletal muscle dysfunction&lt;sup&gt;[6,21]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF-α)</td>
<td>Metabolic and skeletal muscle dysfunction (SMD)&lt;sup&gt;[113,114,139]&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Cachexia in COPD&lt;sup&gt;[6]&lt;/sup&gt;</td>
</tr>
<tr>
<td>CXCL8 (IL-8) and other CXC chemokines</td>
<td>Neutrophil and monocyte recruitment and also contributes to SMD&lt;sup&gt;[6]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adipokines such as leptins</td>
<td>Possible role in cachexia in COPD&lt;sup&gt;[6]&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Acute-phase proteins</strong></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Raised in infective exacerbations potentiates cardiovascular effects and SMD&lt;sup&gt;[5,118]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Cardiovascular complications&lt;sup&gt;[40,41]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surfactant protein D</td>
<td>Derived from lung tissue; is a good marker of lung inflammation&lt;sup&gt;[248]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum amyloid A (SA-A)</td>
<td>Released by circulating proinflammatory cytokines, SA-A levels are raised during acute exacerbations of COPD and its concentrations are correlated with the severity of exacerbation&lt;sup&gt;[6,249]&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Circulating cells</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Inverse correlation between neutrophil numbers in the circulation and FEV&lt;sub&gt;1&lt;/sub&gt;&lt;sup&gt;[250]&lt;/sup&gt;, increased turnover in smokers, enhanced production of reactive oxygen species&lt;sup&gt;[251]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Increase macrophage accumulation in the lungs with defective phagocytic property, increase matrix metalloproteinase-9 production compared with nonsmokers&lt;sup&gt;[252]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Increased apoptosis of peripheral T lymphocytes from COPD patients, with increased expression of Fas, TNF-α, and transforming growth factor β&lt;sup&gt;[6,253]&lt;/sup&gt;, increase in apoptosis of CD8&lt;sup&gt;+&lt;/sup&gt; T cells in COPD&lt;sup&gt;[254]&lt;/sup&gt;</td>
</tr>
<tr>
<td>Natural killer (NK) cells</td>
<td>Reduction of cytotoxic and phagocytic function of circulating NK cells has been reported in COPD&lt;sup&gt;[6,255]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Fig. 5. (A) Box plot (log scale) of the different biomarkers determined at baseline in COPD patients, smokers with normal lung function (S), and nonsmokers (NS). IL, interleukin; TNF, tumor necrosis factor. (B) Proportion of patients with no, 1, or 2 (or more) biomarkers (white blood cell count, C-reactive protein, interleukin-6, and fibrinogen) in the upper quartile of the COPD distribution, at baseline (left bars) and after 1 year of follow-up (right bars). (From Agusti A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012;7(5):e37483.)
Numerous studies have provided evidence of systemic inflammation in COPD patients, as shown by the presence of inflammatory mediators such as acute-phase proteins, as well as markers of oxidative stress and immune responses that are increased in the peripheral blood in COPD patients in comparison with smokers who have not developed the disease.\textsuperscript{231–233}

However, the presence of systemic inflammation is poorly defined in COPD patients; most studies have been cross-sectional and indicate that not all COPD patients have a systemic inflammatory response. Systemic inflammation, as already discussed, is a known risk factor for developing many of the conditions described conventionally as comorbidities of COPD.\textsuperscript{222,231,234,235} Smoking, a major cause of airway inflammation in COPD, is known to be associated with systemic inflammation, and is a potential link between the pulmonary and systemic inflammation in COPD and its comorbidities.\textsuperscript{232,236–240} Smoking and reduced FEV\textsubscript{1} also have been found to have an additive effect on systemic inflammatory markers.\textsuperscript{241}

While increasing evidence suggests that the systemic inflammatory pathway provides the common link between COPD and its comorbidities,\textsuperscript{234,236,239,242} the mechanisms by which the systemic inflammation arises are unclear. There is much debate around whether the systemic inflammation in COPD arises from a spill-over of inflammatory mediators from lung inflammation,\textsuperscript{6,231,243} or whether the systemic inflammation in COPD represents a systemic component of the disease that develops in parallel with, or before, pulmonary inflammation.\textsuperscript{231,243} The absence of a relationship between inflammatory biomarkers in the sputum and blood of COPD patients has provided some evidence against the spill-over theory.\textsuperscript{231,237,244} Smoking, lung hyperinflation, tissue hypoxia, skeletal muscle, bone marrow stimulation, immunologic disorders, and infections are all cited as possible sources of systemic inflammation as seen in COPD.\textsuperscript{231,242,245}

Several studies and meta-analyses have shown that in patients with stable COPD there are often elevated levels of systemic inflammatory markers, such as increased circulating leukocytes, CRP, IL-6, IL-8, fibrinogen, and TNF-\textgreek{z}.\textsuperscript{233,234,245–247} Table 4 summarizes the various inflammatory mediators as described in COPD.

However, the prevalence of systemic inflammation in COPD has not been well studied, and many of the earlier published data are derived from short-term, cross-sectional studies with small sample sizes.\textsuperscript{256} These studies show a wide intersubject validation in systemic biomarkers. Moreover, there is no agreed consensus on the type, number, and value of inflammatory biomarkers needed to define systemic inflammation. These cross-sectional studies are unable to fully establish the relationship between biomarkers and key health outcomes, owing to the chronic nature of COPD and its comorbidities. Data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study\textsuperscript{257} in more than 2000 COPD patients, control smokers, and nonsmokers assessed longitudinally over 3 years was used to evaluate systemic inflammatory biomarkers. Many systemic inflammatory biomarkers were found to be reproducible over time, with fibrinogen being the most repeatable.\textsuperscript{258} As shown in other studies, differences in several biomarkers can be shown between COPD subjects and control smokers and nonsmokers, including peripheral white blood cell count, IL-6, CRP, and fibrinogen, despite large variability within each group (Fig. 5A), whereas others such as IL-8 and TNF-\textgreek{z} appear to be higher in smokers than in COPD patients.\textsuperscript{20} When the proportion of COPD patients with 0, 1, or 2 (or more) of these biomarkers (white blood cell count, high-sensitivity CRP, IL-6, and fibrinogen) were in the upper quartile of the COPD distribution, 28% of patients had 2 or more of these biomarkers elevated at the time of recruitment and 56% of these subjects still had 2 or more systemic inflammatory biomarkers elevated at 1 year (see Fig. 5B), whereas 43% of patients had no raised systemic inflammatory biomarkers at baseline and 70% of these patients still had none of the systemic biomarkers elevated at 1 year. Thus, from this study and according to this definition, approximately 16% of COPD patients have sustained systemic inflammation. Those patients with sustained systemic inflammation...
inflammation were more breathless, with poorer exercise capacity, higher exacerbation rate, and higher mortality. Those patients with sustained systemic inflammation had a higher prevalence of cardiovascular disease. This study therefore suggests that there may be a systemic inflamed COPD phenotype of COPD, which can be described as a phenotype of COPD because it only occurs in a percentage of patients, is stable over time, and is associated with clinical and functional characteristics and poor clinical outcomes. It is possible that targeting these individuals with appropriate treatment may improve outcomes.

Vanfleteren and colleagues looked at 213 COPD patients with the aim of clustering 13 clinically identified comorbidities, and to characterize the comorbidity clusters in terms of clinical outcomes and systemic inflammation. A total of 97.7% of all patients had 1 or more comorbidities and 53.5% had 4 or more comorbidities. Five comorbidity clusters were identified: (1) less comorbidity, (2) cardiovascular, (3) cachetic, (4) metabolic, and (5) psychological. An increased inflammatory state was observed only for TNF receptors in the metabolic cluster and for IL-6 in the cardiovascular cluster, suggesting a role for low-grade systemic inflammation in the pathogenesis of COPD comorbidities.

Fig. 6 summarizes the interrelation between inflammation and the comorbidities and systemic effects as observed in COPD, although some of the effects described as systemic could also be interchangeably described as comorbidity, as described earlier.

SUMMARY

The extrapulmonary effects of COPD are truly multifarious, and have an adverse effect on function and outcomes in COPD.

Fig. 7 summarizes the impact of comorbidities on all-cause mortality in COPD patients.

The clinical management of this condition should therefore be directed toward identifying and treating these extrapulmonary effects, which may lead to improved outcomes for this condition. Novel therapies particularly targeted toward the inflammation associated with COPD should be developed.

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