Comorbidities and Systemic Effects of Chronic Obstructive Pulmonary Disease

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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.

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]

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Clin Chest Med 35 (2014) 101–130
http://dx.doi.org/10.1016/j.ccm.2013.10.007

Table 1
Observed systemic effects and comorbidities in the COPD population

Systemic Effects of COPD[4–6]	Comorbidities in COPD[4–6]
Muscle dysfunction	Cardiovascular disease
Cachexia	Lung cancer
Anemia	Osteoporosis
Muscle dysfunction	Diabetes
Autonomic dysfunction	Psychological issues: anxiety/depression
Systemic inflammation	Obstructive sleep apnea

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 colleagues[11] 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 colleagues[12] 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 (FEV_1) is also known to be an independent predictor of cardiovascular complications in COPD patients. In the Lung Health Study, for every 10% decrease in FEV_1, cardiovascular mortality increased by approximately 28% and nonfatal coronary events increased by approximately 20% in mild to moderate COPD.[10] 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]

^{18}F-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.[26]