Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Review

Defining COPD-Related Comorbidities, 2004-2014

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Abstract

Chronic obstructive pulmonary disease (COPD) is a disease of aging in combination with genetic, environmental, and behavioral risk factors. Aging and many of these risk factors are shared with other diseases, and, as a result, it is not surprising that patients with COPD often have coexistent diseases. This review of COPD comorbidities uses a framework in which coexistent diseases are considered important comorbidities if they are more frequent, have more severe consequences, influence the progression and outcomes of COPD, or are clustered together into proposed phenotypes, supplemented by a framework in which certain comorbidities are expected to share specific pathogenic mechanisms. This review explores classic COPD comorbidities such as cardiovascular disease, cachexia and sleep apnea, but also looks at more recently described comorbidities, such as gastroesophageal reflux, osteoporosis and depression/anxiety.

Abbreviations: health-related quality-of-life, **HR-QOL**; forced expiratory volume in 1 second, **FEV_1**; National Health and Nutrition Examination Survey, **NHANES**; relative risk, **RR**; odds ratio, **OR**; Global Initiative for chronic Obstructive Lung Disease, **GOLD**; body mass index, **BMI**; hazard ratio, **HR**; C-reactive protein, **CRP**; tumor necrosis factor, **TNF**; relative risk, **RR**; interleukin-6, **IL-6**; confidence interval, **CI**; computed tomography, **CT**; gastroesophageal reflux disease, **GERD**; atrial fibrillation/flutter, **fibrillation**; benign prostatic hypertrophy, **BPH**; coronary artery disease, **CAD**; congestive heart failure, **CHF**; chronic renal failure, **CRF**; cerebrovascular accident, **CVA**; degenerative joint disease, **DJD**; gastroesophageal reflux disease, **GERD**; obstructive sleep apnea, **OSA**; peripheral artery disease, **PAD**; pulmonary hypertension and right heart failure, **pulmonary HTN/RHF**; coronary heart disease, **CHD**; chronic kidney disease, **CK**

Funding: Not applicable
Date of Acceptance: February 27, 2014
Citation: Martinez CH, Miguel DJ, Mannino DM. Defining COPD-related comorbidities, 2004-2014. *JCOPDF*. 2014; 1(1):51-63. doi: http://dx.doi.org/10.15326/jcopdf.1.1.2014.0119.

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Keywords:

chronic obstructive pulmonary disease; comorbidity; cardiovascular disease; chronic illness

Introduction

Over the past 60 years we have witnessed radical transformations in population demographics and the burden of diseases that are shaping health care and which have an immediate and future impact within the field of respiratory diseases. Despite improvements in life expectancy and lower death rates in the United States over this period, COPD rose to the third leading cause of death in 2008, a testament to the growing importance of chronic diseases and disability.[1] Refinements in the understanding of the pathophysiology and mechanisms responsible for susceptibility and heterogeneity of COPD (reviewed in other articles in the same issue of this journal) have occurred over the past 10 years. The search for additional ways to modify important outcomes has been enriched by two separate but related concepts that, at the turn of the century, were not always part of the mainstream

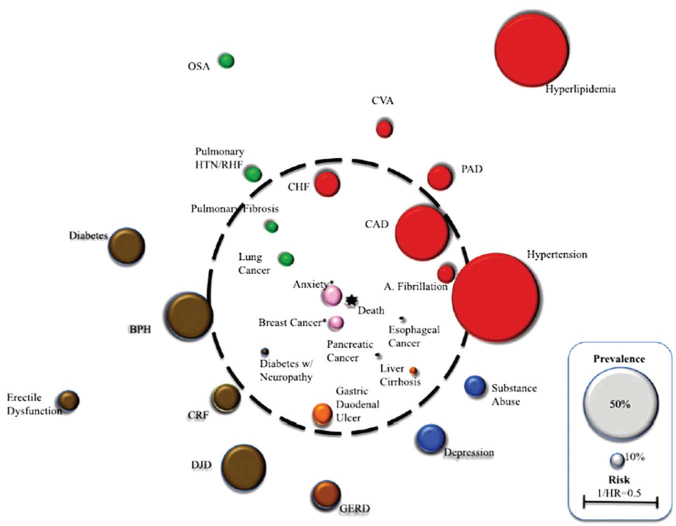

Figure 1. The Comorbidome: A Graphic Expression of Comorbidities With More Than 10% Prevalence in the Entire Cohort[a]

The *comorbidome* is a graphic expression of comorbidities with more than 10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio [HR], .1; 95% confidence interval, .1; $P < 0.05$). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted orbit (1/HR ,1). Bubble colors represent organ systems or disease clusters (cardiovascular = red, female-specific comorbidities = pink, pulmonary = green, psychiatric = blue, others = brown and orange).

[a]Reproduced with permission from Am J Respir Crit Care Med[7]

understanding of the disease. The first one is that the degree of obstruction – which defines the disease and its severity – does not fully correlate with COPD outcomes (exacerbations, death, and health-related quality-of-life [HR-QOL]).[2,3] The second is that a bidirectional interplay exists between the persistent inflammatory processes damaging the lungs and other organs. As a result, COPD is a complex disease linked with other comorbidities that influences treatment effectiveness and outcomes. This paper presents a review of the importance of COPD comorbidities in the development, progression, prognosis and therapy of COPD, and identifies the gaps in knowledge and research in this area.

Challenges in the Identification and Interpretation of COPD Comorbidities

In the United States, COPD patients are usually older adults who have a history of tobacco exposure. These traits are shared with other chronic conditions, including cardiovascular disease and cancer. The typical patient with COPD reports, on average, 4 or more additional diseases[4] and on any given day one-third of COPD patients use 5-10 different medications.[5] There are several different frameworks that can help to decide if the relevance of a *coexistent disease* could be elevated to that of a significant *comorbid interaction*: These are either:

1. When there is a mutual impact of one disease on the other's outcomes[6];
2. When the frequency and impact on mortality surpasses the expected within the general population[7]; *or*
3. When the presence of the disease is part of unique COPD phenotypes.[8]

In keeping with these frameworks, we present those comorbidities which fulfill at least one of the characteristics. There is, however, significant heterogeneity in the definitions of each one of these studied diseases and the source of data used to evaluate the associations between it and COPD. When possible, we describe the source of information, recognizing that each design has the ability to examine different elements of the entire picture. In the absence of controlled intervention studies to determine the ultimate value of finding and treating comorbidities, consistency across research designs is one of the most valuable aspects of observational data. Thus, at this time, the available data allow us to advance only limited therapeutic recommendations. Each section of this review summarizes the evidence in favor of the association between the disease and COPD, the potential mechanisms, the impact of each disease on COPD outcomes, and the therapeutic implications.

Cardiovascular Disease

Longitudinal population-based studies show that low lung function, measured by forced expiratory volume in 1 second (FEV_1), is associated with cardiovascular mortality. Participants in the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study with the lowest levels of FEV_1 showed 5 times higher risk of death by ischemic heart disease. A pooled analysis of similar longitudinal studies determined that for every 10% decline in FEV_1, cardiovascular mortality increases by 28% showing a clear relation between overall cardiovascular death and low lung function.[9] A similar gradient exists if the analysis is limited to those fulfilling the diagnosis of COPD. Combined data from more than 5,000 participants in 2 cohorts (the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study) showed that while the odds ratio (OR) of having cardiovascular disease is 1.7 (95% confidence interval [CI] 1.5-1.9) for those in the Global Initiative for chronic Obstructive Lung Disease (GOLD) spirometry category 1, it increased to 2.2(95% CI 1.9-2.5) for those in GOLD 2, and 2.4(95% CI 1.9-3.0) in GOLD spirometry stage 3-4.[6] Of note, the association has been shown to be present for the whole spectrum of cardiovascular diseases, including cerebrovascular disease, congestive heart failure and arrhythmias, and is present even in early disease stages.[10] For example, heart failure was self-reported among 12.1% of participants with COPD in NHANES 1998-2008 (compared with 3.9% of those without COPD) and among 7% of participants in other large cohort studies.[2] In general, most studies of cardiovascular comorbidities have been able to adjust for age, body mass index (BMI) and tobacco exposure.

At the individual level, comorbid ischemic cardiovascular disease among COPD patients in stable clinical state is associated with a poorer HR-QOL and more severe dyspnea, as Patel, et al, demonstrated in a cohort of more than 300 individuals.[11] In that study, while the frequency of exacerbations was not affected by coexistent ischemic disease, the length of exacerbations was longer. The effect of ischemic heart disease on COPD mortality was confirmed by Divo, et al,[7] after following 1,664 patients for more than 4 years (hazard ratio [HR] for mortality – 1.3). They also showed an increased risk from congestive heart failure (HR 1.3), and atrial fibrillation (HR 1.6). Putcha, et al,[12] in an analysis using NHANES data, detected worse health status due to cardiovascular comorbidities in COPD; the risk of self-rating their health status as poor was higher when individuals had coexistent heart failure (OR 3.8, 95% CI 2.3-6.2) and coronary disease (OR 2.4) (Figure 2). COPD exacerbations are also related to an increase in cardiovascular events, with a risk of myocardial infarction increasing more than 3 times, and the risk of heart failure more than 10 times in the 6 months following an exacerbation.[13, 14]

Multiple mediators and mechanisms are common to COPD and cardiovascular diseases, with evidence pointing to the importance of inflammatory mediators such as C-reactive protein (CRP) or tumor necrosis factor (TNF). Some examples include compromised vasodilation (both flow-enhanced and nitrogen-dependent) in COPD individuals with higher CRP, blood cell count, or with higher emphysema percentage,[15-17] and presence of ultrasound-identified atherosclerotic changes among smokers, which are more pronounced when there is established airway obstruction.[18] The common mediators hypothesis has led to speculation that appropriate control of cardiovascular-related inflammation could improve outcomes in COPD. Findings from observational studies showing lower mortality among COPD patients using statins[19] motivated divergent and precautionary opinions,[20] and led to the design of clinical trials which are still in progress.[21] Conversely, beta-blockers, a mainstay of treatment for cardiovascular disease, are frequently denied to

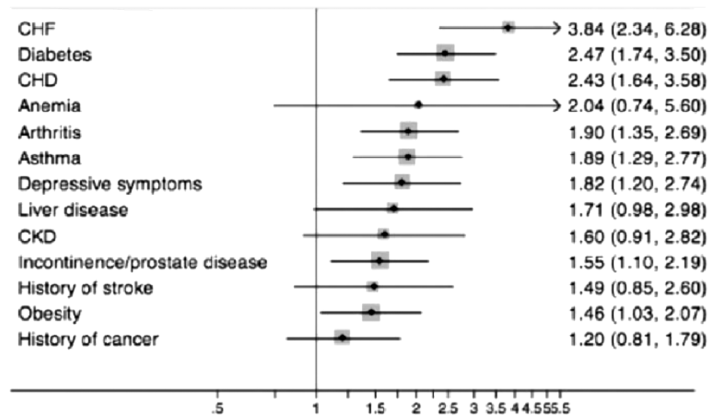

Figure 2. Graphic Representation of the Impact of Different COPD Comorbidities on HR-QOL[a]
The arrow represents the odds ratio (OR) for reporting worse self-rate health status among *COPD* patients with each condition from participants in NHANES 2001-2008.
[a]Adapted with permission from *COPD* journal[12]

COPD patients due to concerns about worsening bronchospasms. This occurs despite support for their use in COPD patients in the cardiovascular literature and guidelines and the absence of studies demonstrating adverse effects.[22-24] With both COPD and cardiovascular disease more common in the elderly, the cardiovascular safety of inhaled medications remains a valid question. There is no evidence of increased cardiac risk for participants in recent studies of long-acting beta-agonists[25,26] or long-acting anti-muscarinic agents,[25-27] but there is a signal of increased cardiovascular risk shortly after introduction of any long-acting COPD medication in observational studies.[28,29]

Diabetes and Metabolic Syndrome

Nationally-representative cross-sectional studies in the United States have estimated a prevalence of diabetes of 12.7% to 16.3% among patients with COPD, significantly higher than in the general population.[6] Longitudinal studies have confirmed that COPD is a risk factor for incident diabetes (RR of 1.4-1.8).[30,31] The association of the cluster of risk factors known as *metabolic syndrome* (hypertension, hyperglycemia, hyperinsulinemia, abdominal obesity), an early step in the development of diabetes and vascular disease, with low levels of lung function, has been well established.[32] This finding has fostered the search for common mediators, a fertile area in which the role of adipokines is still being defined. For example, in COPD the level of visceral fat is associated with higher levels of interleukin-6 (IL-6) and lower levels of adiponectin,[33] and COPD patients have more insulin resistance, whose magnitude is related to the levels of (IL-6) and TNF-α. The use of corticosteroids in COPD and incident diabetes is still a subject of debate, with pooled data from clinical trials showing no significant associations (HR 1.0, 95% CI 0.7-1.5),[34] but with analyses of administrative data supporting a risk (RR 1.3, 95% CI 1.3-1.4).[35] For those individuals with both COPD and diabetes, the risk of death is higher at 5 years,[6] especially when they are recovering from an exacerbation (HR 2.2),[36] and the risk of poor health is also higher.[12] High dose inhaled corticosteroids have also been associated with a higher frequency of diabetes-related hospital admission,[37] and higher glucose levels.[38]

Osteoporosis

Both osteopenia and osteoporosis are increased among patients with COPD, with the severity of COPD related to the prevalence of osteoporosis. Analyses of large administrative databases have estimated that a new diagnosis of COPD increases the risk of being diagnosed with osteoporosis threefold.[39] Osteoporosis in COPD can also be found among those with less severe airway obstruction. The clinical consequences of osteoporosis, fractures, are also more frequent in COPD individuals, especially in those with more severe obstruction. Interestingly, the associations are as strong or stronger for men than for women and include a rapid progression of bone loss, in particular when vitamin D deficiency coexists.[40] The mechanisms of the COPD-osteoporosis association go beyond the effect of age and systemic steroids, as those factors have been appropriately controlled in the available studies. The classic explanation of osteoporosis in COPD as a result of accelerated decline in bone mineral density among users of inhaled corticosteroids is not supported by recent clinical trials with appropriate follow-up.[41] The consistent finding of an association, not just between COPD and osteoporosis, but between the severity of radiologic emphysema and low bone mineral density,[42,43] points to a common mechanism of bone and lung destruction. Interesting associations have been made between the activity of markers of osteoclast activation (e.g. matrix metallo proteinases) and lung function. The clinical implications of the high frequency of osteoporosis in COPD are significant. Physicians are not accustomed to screening men for osteoporosis, thus, more than 80% of COPD individuals with osteoporosis are undiagnosed and untreated.[39,44] In addition, COPD is a risk factor for death and perioperative complications after hip fracture repair, highlighting the importance of early diagnosis and prevention of bone loss in this population.

Cachexia and Muscle Wasting

Low body mass index (BMI) and weight loss is common in many chronic diseases; however, in COPD the picture is more complex, as low weight is due to a disproportionate loss of fat-free tissue, especially muscle mass. Low fat-free mass indices, below 15 kg/m^2 in women and 16 kg/m^2 in men, are found in 20%-50% of COPD patients and double the risk of death.[45] The mechanisms explaining cachexia in COPD are still unclear,[46] but go beyond the classic explanation of an increase in the oxygen cost of breathing,[47] or the pro-inflammatory effect of hypoxemia,[48] as cachexia can be present in normoxemic individuals and does not have a linear association with measures of respiratory mechanics. Decreased appetite could be an explanation, but the majority of supportive data comes from cross-sectional studies, where cachexia is already established. Similarly, in cachectic individuals, mediators of catabolic state are upregulated.[49] Cachexia is associated with the degree of computed tomography (CT)-measured emphysema, but not the severity of the airway involvement.[50,51] Biologic plausibility for this association has been strengthened by metabolomic studies showing similar profiles of amino acid metabolism in those with either emphysema or cachexia,[52] and an association between cachexia in COPD individuals and specific genetic polymorphisms within genes related to fat mass and obesity.[53] Although low BMI is a prognostic factor in COPD, and is part of multidimensional prognostic indices,[54] there is limited information on the management of patients with cachexia, including the potential for drug interactions and abnormal metabolism,[55] and the effect on cost and health service utilization.[56,57] Potential interventions including the use of mechanical ventilation (to decrease the energy expenditure of breathing), nutritional supplementation,[58] anabolic steroids and growth hormone releasing factors such as ghrelin (to counterbalance the switch from catabolism to anabolism), have met with mixed results.[59,60] Fortunately, COPD patients with cachexia improve with pulmonary rehabilitation similar to their well-nourished counterparts.[61,62] Beta-2 agonists, one of the most widely used treatments for COPD, have proven to have positive effects on skeletal muscle function and structure in animal models studying different muscle-wasting diseases, but at doses beyond that used in clinical practice.[63]

Anemia

Anemia has been described with variable frequency in the COPD population, from 3.3% in NHANES to 6.2% among COPD outpatients, and up to 17% among COPD inpatients.[64-66] It has been hypothesized that anemia in COPD shares mechanisms with other anemias of chronic disease,[67] with persistently elevated interleukins (especially IL-1) interfering with the response to erythropoietin. A recent cross-sectional study found higher levels of erythropoietin in COPD patients with anemia, compared with those with normal hemoglobin.[68] Different COPD outcomes, including poor functional status,[64] frequent exacerbations[69] and increased health care-related direct and indirect costs[70] have been associated with the presence of anemia. Cohort studies suggest that survival also seems to be affected by the hemoglobin level, being lower in those with anemia than in those with a normal level or polycythemia.[71] No specific treatment recommendations for coexistent anemia in COPD are currently available.

Obstructive Sleep Apnea

Population-based studies have identified sleep apnea among COPD patients with a frequency similar or just slightly higher than the general population: between 8% and 14%.[72,73] The similar frequency and distribution of risk factors has limited the ability to formulate and prove hypotheses about specific mechanistic pathways in the association. However, what is unique about this form of *overlap syndrome* is the increase in mortality for those with untreated sleep apnea, and the ability to modulate the risk with regular use of therapy for sleep apnea.[74] Clinical findings that should prompt an evaluation of sleep apnea include pulmonary hypertension or right heart failure unexplained by or out of proportion to the degree of obstruction.

Gastroesophageal Reflux Disease

Although researchers have used many different definitions of gastroesophageal reflux disease (GERD), including validated questionnaires,[75-77] esophageal pH-monitors,[78] and administrative medical claims data,[79] there is a consistently higher prevalence of the disease among those with COPD than in the general population. The findings are also consistent across different designs and populations, including cross-sectional studies of COPD patients reporting prevalence between 16% and 62%,[80] and population-based representative surveys describing a prevalence of 28%.[79] There is, however, limited evidence concerning the direction of the relation. One study of the United Kingdom General Practice Research Database detected a low frequency of receiving a new diagnosis of COPD after a diagnosis of GERD was established, but a higher frequency of incident GERD diagnosis among those with established COPD.[81] Those findings, plus the identification of GERD more frequently among COPD individuals with predominantly bronchitis phenotypes (33.6% compared to 27.6% in those without chronic bronchitis),[51] have created renewed attention to the role of mechanical factors such as persistent cough, changes in thoracic and abdominal pressures and the development of hiatal hernias (present in 13% of COPD individuals)[82] as explanations for the COPD-GERD association. All of the above theories are still to be explored. Almost all COPD outcomes are impacted by coexistent GERD, including poorer HR-QOL and more severe symptoms.[83,84] The risk of frequent exacerbations with coexistent GERD has been reported with an OR of 1.7(95% CI 1.4-2.0)[85] in a large cohort study, to an OR of 1.5(95% CI 1.5-1.6) in cross-sectional analysis of administrative databases[79] to a RR of 1.9(95% CI 1.3-2.8) to 2.2 in smaller cohorts.[76,86] Observational data has shown better HR-QOL in those with treated GERD,[83] and only one clinical trial has addressed the question of treating COPD with proton-pump inhibitor medications and the risk of exacerbations[87]; their results (77% reduction of exacerbations) have not been replicated or extended in subsequent analysis or trials; thus, specific therapeutic recommendations are not available.

Anxiety and Depression

The investigation of sensitive aspects of human behavior, such as the presence of anxiety and depression, is challenging when dealing with large population samples. But even when the sample is more limited, such as when participants are clinical patients or volunteers in cohort studies, the multitude of instruments available makes determination of estimates difficult. Still, while the estimates of anxiety and depression in COPD vary widely, the high prevalence of these comorbidities is a consistent finding. In population-based studies, such as NHANES, depression is reported by 20.6% of participants with COPD (compared with 12.5% for those without).[88] An incident diagnosis of COPD increases the risk of being diagnosed with depression (RR 1.8, 95% CI 1.7-2.0), and the risk appears to be higher within the first year after diagnosis.[89] Nationally-representative data from adults 50 years of age and older in the United States have found that up to 40% of those with COPD have depressive symptoms, a proportion higher than what is found in other chronic diseases, such as stroke, diabetes and heart disease.[90] In a series of clinical patients or volunteers the frequency has been reported between 26%[91] and 35%.[92] Depression is more common in women with COPD, and in younger individuals, along with those with lower educational achievements and current smokers.[90,91] Other effects include shorter 6-minute walk results,[91] lower self-reported HR-QOL,[12] and twice the mortality rate.[94,95]

Anxiety has been reported by 8.6% of NHANES participants with COPD (in contrast with 3.8% for those without COPD), and up to 28% in clinic-based series[88,96]; it has been associated with female gender[97] and chronic bronchitis symptoms. Unexpectedly, anxiety in COPD has been associated with more, not less, levels of physical activity at baseline,[98] and previous reports of a lower walking distance in these subpopulations could be mediated just by the low pulmonary function in participants with anxiety.[99] Equally important is that there is an increased risk of being diagnosed with COPD after a diagnosis of anxiety (RR 1.6, 95% CI 1.4-1.9), depression (RR 1.8, 95% CI 1.5-2.0), or both (RR 2.1,95% CI 1.7-2.5).[100] Anxiety increases the risk of death among COPD patients.[7]

The role of pharmacologic and other therapies including cognitive and behavioral interventions, for the treatment of anxiety and depression is still unclear.[101] Fortunately, rehabilitation programs could improve symptoms of anxiety and depression,[102] and referral to specific mental health services has demonstrated improved mortality.[103]

Clustering Comorbidities Based on Common Mechanisms

COPD is very heterogeneous and multiple mechanisms have been implicated in its pathogenesis. These mechanisms include inflammatory, immune, senescent, and reparative pathways. Cigarette smoke is associated with inflammatory changes, with an intensity and persistence that is more marked in smokers with COPD, and with progression from an initial response, secondary to activation of the innate immunity, to enhancement of the adaptive immune response as the disease progresses, analogous to what happens in autoimmune diseases.[104-106] As a result, multiple mediators, including cytokines and non-specific inflammatory mediators, are elevated, both in the lung, as well as in the systemic circulation. Patients with COPD and comorbidities have higher levels of these mediators. However, it is still difficult to know if the systemic effect of the extrapulmonary disease involves the lung, or if the excess of mediators produced in the lung is spilling over into the circulation. The key COPD comorbidities with inflammatory and immune features include cardiovascular disease,[16,17] osteoporosis[16,17,107] and the metabolic syndrome and its consequences, including diabetes.[33,108,109] Persistent elevation of inflammatory markers (CRP, fibrinogen, and leukocyte count) is also related to COPD exacerbations, even in the absence of an exacerbation history.[110]

The description of COPD as an accelerated senescence of the lung[111] has fostered further research into the role of abnormal apoptosis in the pathogenesis of COPD. Abnormal telomere shortening is associated with COPD.[112,113] Comorbidities associated with abnormal telomere function include accelerated weight loss (fat-free mass and muscle mass loss, in particular),[114] and can be found in early stages of COPD.[115] Osteoporosis[116,117] and cardiovascular disease[118-120] are other examples of diseases sharing a significant role of accelerated aging mechanisms with COPD.

Abnormal repair and abnormal responses to enhanced oxidative stress are also potential mechanisms for the development of COPD,[121-123] which are shared with pulmonary fibrosis and cancer. While the development of interstitial lung diseases, especially pulmonary fibrosis, was previously seen as diametrically opposite to COPD, findings of large cohorts of COPD patients with detailed imaging evaluation have found that early interstitial abnormalities are common,[124] and that the combination of emphysema and pulmonary fibrosis is a disease with specific clinical characteristics and prognostic implications.[125] Other pathogenic mechanisms, not covered here, including abnormalities in the coagulation pathway, autoimmunity and abnormal cell proliferation, and the recently introduced role of the change in bacterial communities in the lung (microbiome),[126] will continue bringing exciting ideas to the interpretation of clusters of COPD comorbidities.

Comorbidity Clusters in COPD Phenotypes

The improving definition of COPD phenotypes continues to enhance our understanding of COPD-related comorbidities.[8] Burgel, et al, used hierarchical cluster analysis of data from more than 500 patients and detected 3 main groups: one with COPD but low burden of comorbidities; a second one with high risk of comorbidities with severe emphysema, low frequency of cardiovascular comorbidities and low BMI.; and a third with high risk of mortality, mainly due to a high

Table 1: Clusters of COPD Comorbidities Based on Common Pathogenic Mechanisms

1. **Inflammation/ Immune Response** – Asthma, pneumonia, IHD, osteoporosis, musculoskeletal dysfunction, metabolic syndrome
2. **Apoptosis/Necrosis/Degeneration** – Cardiovascular diseases, malignancies, metabolic syndrome, osteoporosis, musculoskeletal dysfunction
3. **Trauma and Repair/Cell Proliferation and Neoplasia/Fibrosis** – Malignancies, musculoskeletal dysfunction
4. **Thrombosis/Hemorrhage** – Pulmonary embolism, ischemic heart disease, cerebrovascular diseases
5. **Unknown** – Depression, chronic renal failure

Table 2. Summary of Evidence Regarding the Frequency, Impact, Phenotypic Associations and Areas of Uncertainty Around the Reviewed COPD Comorbidities[a]

Comorbidity	Best Epidemiologic Evidence	Impact on COPD Outcomes	Mechanistic Pathways	Associated Phenotypes	Areas of Uncertainty
Cardiovascular Disease	Longitudinal studies, including population-based	Mortality QOL Duration of exacerbation Frequency of exacerbations?	CRP, TNF	Airway predominant	Role of cardiovascular medications Risk of COPD medications in cardiac disease
Diabetes	Longitudinal studies, including population-based	Mortality QOL	IL-6, TNF Adipokines?	Airway predominant	Risk of COPD medications in patients with diabetes Role of adipokines
Osteoporosis	Longitudinal studies, including population-based	QOL	Metallo proteinases	Emphysema predominant	Mechanisms Implementation of preventive strategies
Cachexia	Longitudinal studies	QOL	Upregulators of catabolic state Genetic polymorphysms	Emphysema predominant	Therapy
Anemia	Population-based	QOL Exacerbations Mortality?	IL-1 Poor response to erythropoietin?		Therapy
Obstructive Sleep Apnea	Population-based	Frequency of associated pulmonary hypertension	Unclear		
GERD	Population-based	QOL Exacerbations	Hiatal hernia? Aspiration?	Frequent exacerbator	Mechanisms Impact of therapy
Anxiety and Depression	Longitudinal studies	Mortality QOL Physical activity	Unclear		Mechanisms Role of gender and social disparities Therapy

[a]Detailed descriptions and references found within the text

burden of cardiovascular disease, in the presence of less emphysema.[127] Detailed population-based cluster analysis, based on data from the entire population of Switzerland, reported that emphysema clusters with cachexia, and chronic bronchitis clusters with diabetes and obesity.[128] This confirms the clinical observation of the phenotypic coexistence of emphysema with low BMI and osteoporosis, and that the chronic bronchitis phenotype tends to present with more diabetes and sleep apnea. Follow-up of a cohort of 342 patients for more than 4 years allowed Garcia-Aymerich, et al, to identify 3 different COPD phenotypes. One of the phenotypes with high frequency of obesity, diabetes and cardiovascular disease had more frequent admissions with cardiovascular problems.[129] Another proposed COPD phenotype, the frequent exacerbation phenotype, is also associated with a limited number of diseases including GERD, cardiovascular disease and depression.[85,130] One final concept that deserves discussion and further research is the role of low physical activity as a common end-pathway of COPD comorbidities. Overall most of the diseases described above are associated with a sedentary lifestyle, and will force the patient to become more inactive, which amplifies the inflammatory effect of COPD and the coexistent diseases.[131,132] Determining if exercise programs, not just pulmonary rehabilitation, can modulate the inflammatory response is currently the subject of intense research.

Conclusions

Among COPD patients, there is growing evidence that some coexistent diseases cannot be explained solely by common risk factors (e.g., tobacco exposure in the United States) or aging. These diseases are important comorbidities as demonstrated by having a frequency higher than in the general population (such as cardiovascular disease, diabetes, anemia) and having more severe consequences, including impact on mortality (e.g., depression, anxiety, diabetes), HR-QOL (heart failure, GERD), and exacerbations (GERD). COPD also increases the risk of developing comorbidities (GERD, diabetes) or having a negative impact on some of those diseases (osteoporosis). There are also comorbidities which are more frequent among patients with proposed COPD phenotypes. Osteoporosis and weight loss are more frequent in those with emphysema-predominant COPD, while diabetes, high BMI and cardiovascular disease are more common in airway-predominant disease, and GERD is associated with the frequent exacerbation phenotype. Common inflammatory and immune mechanisms link specific diseases with some steps in COPD pathogenesis (development of emphysema and low bone mineral density) (Table 1) and phenotypes (e.g., chronic bronchitis and metabolic syndrome). A better understanding of the relevant pathways should provide better guidance for future therapies (Table 2).

Acknowledgements

All authors contributed equally to the concept, outline, and writing of the manuscript. All authors approved the final version of the manuscript.

Declaration of Interest

CHM and MJD report no conflicts. DMM has received honoraria or consulting fees and served on speaker bureaus for GlaxoSmithKline, Novartis Pharmaceuticals, Pfizer Inc., Boehringer-Ingelheim, AstraZeneca, Forest Laboratories Inc., Merck, Amgen and Creative Educational Concepts. Furthermore, he has received royalties from Up-to-Date and is on the Board of Directors of the COPD Foundation. CHM is supported by funding from NIH/NHLBI Grant # T32 HL007749-20.

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