IN-DEPTH REVIEW: UNRAVELING THE COMPLEXITY OF COPD

COMMENTARY

Revealing the complexity of chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a complex systemic disease, that until recently, was underrecognized, underappreciated, and poorly understood. Bonet first described COPD as early as 1679 when he discussed “voluminous lungs,” and yet it wasn’t until the 1960s that physicians began to create formalized definitions of the clinical syndrome they were encountering.1 These initial definitions focused on either clinical characteristics (such as cough and dyspnea) or anatomic features (such as enlargement of alveolar spaces) and, in some sense, neglected expanded features that could be useful in identifying and understanding the disease.1 Still today, COPD is a defined as “a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.”2 This definition remains broad, describing an “airflow limitation” that, in reality, is caused by distinct features of small-airway disease, chronic bronchitis, and emphysema that may be highly variable among patients despite identical measures of airflow limitation measured by the forced expiratory volume in 1 second (FEV1)/forced vital capacity ratio. Research during the past few decades has begun to reveal a new understanding of the pathophysiology, public health impact, and overall complexity of COPD. This issue of Translational Research contains an in-depth review of COPD that includes 4 articles that serve as illustrative examples of how our understanding of COPD is shifting from a physiologically defined obstructive lung disease caused by cigarette smoking to a complex systemic disease with risk that is modified by multiple factors (including genetics and the environment), has variable manifestations in different populations, is characterized by multiple disease phenotypes, and occurs, not in a vacuum, but in the context of other common comorbid conditions (Fig 1).

COPD is the third leading cause of death in the United States and is the only leading cause of death that is increasing in prevalence.3 Between 1970 and 2002, death...
rates secondary to stroke and heart disease decreased by 63% and 52%, respectively, whereas death rates resulting from COPD increased by 100%. Currently, approximately 14 million Americans have been diagnosed with COPD, although it has been estimated that an additional 12 million individuals remain undiagnosed. By 2030, it is estimated that approximately 9 million people will die annually from COPD. COPD is also a source of significant health expenditure and societal costs. Until recently, patients, clinicians, and researchers undervalued the overwhelming impact of this disease on individuals’ quality of life and society’s economic stability. In 2008, it was estimated that the cost to the United States for COPD and asthma was approximately $68 billion, including $14.3 billion in direct costs and $53.7 billion in mortality costs. In a 2001 international study, it was found that 45.3% of COPD patients younger than 65 years of age had missed at least 1 day of work within the previous year secondary to COPD. In that same study, patients with COPD often minimized their own symptoms; 60.3% of patients who ranked their disease as mild or moderate reported severe breathlessness.

In recognition of the increasing prevalence and costs associated with COPD, during the past decade there has been great progress in our understanding of the pathogenesis, manifestations, and clinical outcomes of this common disease. In this in-depth review issue, we explore and celebrate the strides made while also identifying areas that require further investigation to expand our understanding of COPD. Beginning with a discussion of diet and nutrition, Hanson et al illustrate how vitamins and micronutrients may modify risk of developing lung disease that could introduce a true primary preventative strategy for COPD beyond avoidance of cigarette smoke and environmental pollutants. Aryal et al provide an update on how COPD risk, manifestations, and outcomes differ between men and women, thereby illustrating the complex nature of COPD and pointing out opportunities to personalize therapies further. The insightful review of Bon et al focuses us on the complex nature of COPD and our future ability to personalize therapy by providing a guide for clinical and translational investigators on how to address the many attributes that constitute a disease “phenotype” as we move toward identifying new ways of classifying, studying, and improving the care of COPD. Last, Bhatt and Dransfield, through a detailed review on concurrent cardiovascular disease in COPD, provide an illustrative example of the impacts comorbid conditions have on those living with COPD and why both comprehensive clinical care and clinical investigation in COPD need to account for the many concurrent conditions that impact patient-centered outcomes and mortality.

COPD RISK FACTORS

Although previously understood as a disease almost exclusively of smokers, we now understand that the risk of developing COPD is determined by both the genetic and environment milieu of each patient. Alpha-1-antitrypsin has long been acknowledged as a genetic cause of COPD, although it affects a relatively small proportion of patients. Family association studies have pointed toward other potential genetic causes and, within the past decade, genomewide association studies have begun to identify countless single nucleotide polymorphisms thought to be associated with the development of emphysema and/or COPD. It is now understood that numerous environmental factors impact the development of airway disease. Exposure to biomass fuel smoke from indoor cooking, for instance, has been shown to be a large contributor of...
COPD among individuals in developing countries.\textsuperscript{12,13} Similarly, growing research has begun to show the role of diet and nutrition in protecting against the development of airway disease.

In the first article in this in-depth review of COPD, Hanson et al discuss the rapidly growing field of diet and vitamin D, and their associations with lung function. Their article takes both a micro- and macrolevel view on the role of nutrients in the development of lung disease. It describes how vitamins C and E function as antioxidants in lung parenchyma, as well as how vitamins D and E affect systemic inflammation and lipid phase oxidation. They walk us through data from observational studies, longitudinal studies, intervention studies, and randomized control trials that show numerous associations between the intake of vitamins A, C, E, and D, and carotenoids and improved lung function. Although dietary studies in the past have struggled to show causal relationships, the magnitude of observational research reviewed in this insightful article argues strongly for the development of future prospective research initiatives that test the impact of dietary interventions as a possible means for primary and secondary prevention of COPD.

**COPD PHENOTYPES**

COPD is a heterogeneous clinical syndrome characterized by a variety of concurrent lung and systemic manifestations. Although airflow limitation defines both the presence and stage of disease, this physiologic measurement is not always well correlated with the clinical disease characteristics or outcomes for any given patient. For example, patients with the same degree of airflow limitation, or FEV\textsubscript{1}, have variable clinical outcomes, such as symptoms, exercise tolerance, radiographic features, and prevalence of comorbid conditions.\textsuperscript{14-16} Although some patients have a disease predominately of parenchymal destruction (emphysema), others have more changes to their small airways (peribronchiolar fibrosis). Although all patients are at risk of acute exacerbations of disease, the frequency of exacerbations is not only associated with the severity or stage of disease. Given the great clinical variability of this disease, researchers have begun to define new ways of analyzing and categorizing patients with COPD into “clinical phenotypes,” or subgroups of patients with similar clinical outcomes, to predict prognosis more accurately and to improve treatment.\textsuperscript{15,16}

At a time when COPD has become increasingly prevalent among women, Aryal et al discuss the differences in prevalence, clinical presentation, morbidity, and mortality, as well as treatment implications for women in their article on COPD and gender. This review identifies what could be argued as a separate clinical phenotype because it shows women are more likely to have a clinically different set of outcomes including symptoms, comorbidities, and disease course. Although tobacco use has increased among women during the past few decades, recent studies have found that women may be more vulnerable to the adverse effects of tobacco and show more rapid decline after the onset of disease. Using research from both animal and epidemiologic studies, this review suggests multiple reasons for the differences between men and women in COPD risk, including anatomic differences, behavioral differences, as well as biologic and hormonal differences. In addition to identifying differences in objectively measured risk and disease manifestations, this review also identifies biases still held in medicine that impact both the diagnosis, treatment, and health care utilization of women with COPD.

Growing research focuses on defining new clinical phenotypes within COPD that correspond to clinically different subgroups of patients with differing clinical outcomes, such as lung function data, clinical symptoms, radiographic evidence of disease, or prognosis. Reclassification of this complex disease, however, comes with many challenges of its own. Bon et al focus on the challenges presented to clinicians and investigators alike as we attempt to define COPD phenotypes. They question insightfully whether it is even possible to place patients into well-defined subgroups of disease and question whether COPD, instead, represents a “continuum of varying penetrance” of a number of different clinical features. They also raise the very important issue of how best to select specific populations of COPD patients for clinical studies. For example, many of our largest studies of COPD have focused on those with severe airflow limitation, but because these patients likely have multiple comorbidities, this may blur boundaries between different phenotypes. Instead, we may be better served to focus on mild or subclinical disease in which patients have fewer confounding factors and the concurrent evolution from health to disease for the many potential clinical characteristics of a COPD phenotype could be studied from their earliest stages of development. A similar limitation is presented by the many cross-sectional studies that evaluate patients at only a single time point in a disease such as COPD that is characterized by intermittent exacerbations and progressive decline in lung function, magnifying the need of the research community to develop longitudinal cohort studies in individuals at risk for COPD so the natural history of specific disease phenotypes can be defined from their earliest stages.
COPD COMORBIDITIES

Within the past 10 years, clinicians and researchers have begun to recognize the numerous comorbidities associated with COPD and the mortality associated with patients who carry a diagnosis of COPD. Although COPD is considered the third leading cause of death, more patients with COPD die from their comorbid conditions than from COPD or other respiratory complications. It could be stated that patients do not always die from but rather with COPD. Patients carrying a diagnosis of COPD have higher rates of hospitalization and mortality for all cardiovascular end points, including cardiac arrhythmias, angina pectoris, acute myocardial infarction, congested heart failure, stroke, and pulmonary embolism. The standard mortality ratio for cardiovascular disease among patients with COPD on long-term oxygen therapy compared with the general population is significantly elevated at 7.3. Patients with COPD have increased incidence of and mortality from many other diseases, including osteoporosis, lung cancer, diabetes, dyslipidemia, anemia, and hypertension, even after adjusting for smoking, aging, and use of corticosteroids. To emphasize the significance of these comorbidities, some have even suggested adding a diagnosis of “chronic systemic inflammatory syndrome” to all patients with COPD to reflect more completely the multifaceted nature of COPD as a systemic disease.

In the final article of this review, Bhatt and Dransfield explore the systemic nature of COPD disease as they present the plethora of research and data regarding concurrent COPD and cardiovascular disease. Stepping through the diverse interactions between coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and cardiac arrhythmias, the review analyzes thoughtfully the epidemiologic and pathophysiologic interrelationship among these diseases independent of their often common and shared risk factors. Discussion of multiple population studies showing the link between carotid arterial intimal medial thickness and numerous pulmonary function parameters—including FEV₁, diffusing capacity of carbon monoxide (DLCO), residual volume (RV), and peak expiratory flow rate—help the reader understand the relationship between the pathogenesis of atherosclerosis and COPD. Genetic studies illustrate links between matrix metalloproteinases and glutathione-S-transferase and the development of emphysema and plaque rupture. In addition, discussion of the epidemiologic outcomes of patients with both COPD and cardiovascular disease illustrate the poor prognostic implication of these overlapping clinical entities and provide opportunities for future research and public health interventions.

CONCLUSION

Overall, this in-depth review of COPD steps through emerging research of risk factors for disease, attempts and challenges of better describing and categorizing this disease, as well as the comorbid conditions associated with COPD as we continue to learn about the complexities of this systemic syndrome. This series not only celebrates how far we have come since our early descriptions and definitions of disease, but also it highlights how much is still unknown, and reveals many potential areas for future research.

It is likely that in the decades to come our current understanding of COPD will continue to change and evolve just as it has during the past decade. Many different areas of research as well as varied study designs will be required to understand more completely this disease that varies throughout a population and among individuals during their life span. The current set of reviews provides a framework for areas that are ripe for future investigation as well as points out the challenges with which clinical and translational research communities are faced as we further our understanding of this complex, common clinical entity.

REFERENCES


