The natural history of chronic obstructive pulmonary disease

Historia naturalna przewlekłej obturacyjnej choroby płuc

Abstract

This paper explores the natural history of chronic obstructive pulmonary disease (COPD), including our present understanding of COPD risk factors, phenotypes, and burden, along with COPD progression, including the traditional ‘accelerated lung function decline’ paradigm, to newer paradigms that include other factors. Questions remain unanswered, and there is considerable room for improvement. One of those questions is how the disease should best be defined. While this question has generated lively debate in the literature, it may not be the most important area with regard to advancing our understanding of the disease. The different phenotypes of COPD, particularly with regard to differential interventions and outcomes, is an area that should receive much more attention. Finally, a more holistic view of what comprises COPD progression, looking well beyond the traditional lung function decline paradigm, may also provide additional insights in how to better care for our patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality globally [1]. Understanding the natural history of COPD has been important in the field of pulmonary medicine, dating back to the work of Burrows [2], and Fletcher and Peto [3, 4]. Since then, researchers have championed different hypotheses about COPD development, including the ‘British’ hypothesis that the presence of cough and sputum was the key factor [5] and the ‘Dutch’ hypothesis that the presence of increased airways responsiveness was the major factor [6].

This paper will explore the natural history of COPD, including our present understanding of COPD risk factors, phenotypes, and burden, along with COPD progression, including the traditional ‘accelerated lung function decline’ paradigm, to newer paradigms that include other factors.
COPD definition

The definition of COPD in the Global Obstructive Lung Disease (GOLD) guidelines is: “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases” [7].

Classification of COPD, according to the current criteria, is shown in Table 1 [7]. These guidelines, though, remain controversial. For example, the American Thoracic Society/European Respiratory Society Guidelines for the interpretation of spirometry recommend using a ‘lower limit of normal’ (LLN) approach to classify COPD [8], whereas the ATS/ERS guidelines for COPD recommend using the fixed FEV1/FVC ratio of 70% to classify a person as ‘obstructed’ [9]. While post-bronchodilator lung function is used to classify disease, there is no clear evidence that this works better than pre-bronchodilator lung function. In addition, it is unclear what is the best reference value to use, in that patients may appear ‘normal’ with some and ‘abnormal’ with others [10]. Other areas of controversy include the importance of what was previously called Stage 0 (normal lung function but the presence of chronic respiratory symptoms) and individuals with ‘restrictive’ spirometry (FEV1/FVC ratio of at least 0.70 but an FVC that is less than 80% of the predicted value).

COPD risk factors

Ageing and smoking are the predominant risk factors of COPD in high-income countries [11, 12]. Evidence suggests that exposure to biomass smoke and gases or fumes in the workplace is also important, particularly in the developing world [13, 14]. COPD is a disease with interaction between genetic predisposition and environmental exposures, with studies demonstrating familial clustering [15] and racial/ethnic differences suggestive of a genetic link [16].

COPD phenotypes

The traditional phenotypes that comprise COPD are chronic bronchitis, emphysema, and asthma [17]. Both chronic bronchitis and emphysema can exist concurrently with asthma [18]. The inflammation present in COPD can be differentiated from that seen in asthma, but in some cases where asthma co-exists with COPD it may be difficult to dismiss chronic cough and phlegm purely as symptoms of asthma [18]. A classic Dutch study found that bronchial responsiveness, a hallmark of asthma, leads to the development of COPD [19]. Although this is controversial, other studies have shown that smokers with asthma may lose lung function more rapidly than those without asthma [20].

The traditional COPD phenotypes have become less useful, clinically, in recent years in that they do not help guide therapy for many of our patients, or accurately predict prognosis. This gap has resulted in an attempt to redefine COPD phenotypes with a new paradigm [21]. The underlying concept in this definition is that the collection of diseases we call ‘COPD’ have certain clinical, physiological, and radiological characteristics that define disease, predict prognosis, and better direct therapy. Clinicians have, typically, been using some of these patient characteristics in daily practice to guide therapy (i.e. treating depression in the depressed and treating exacerbations), but there is a great need for standardisation to improve our ability to help our patients.

COPD burden

The burden of COPD comprises several components. These include the number of people who have the disease (prevalence), the impaired quality of life among people with the disease, outcomes of the disease such as exacerbations, hospitalisations and deaths, and costs related to caring for people with the disease.

Prevalence

The prevalence of COPD is estimated in different ways, including self-report of physician-dia-
Diagnosed disease, spirometry with or without a bronchodilator, and questionnaires that ask about the presence of respiratory symptoms [22]. Overall, epidemiological studies from various countries using standardized methods and spirometry estimate COPD prevalence as being between 5% and 25% of the population aged over 40 [12, 22, 23]. The prevalence of COPD is heterogeneous between age, sex, prevalence of smoking, location, and other risk factors [12]. As noted above, COPD prevalence is heavily influenced by ageing, smoking status, and occupational exposures.

**Quality of life**

Another manifestation of the burden of COPD is its effect on health-related quality-of-life measures associated with the presence of disease [24]. Lung function impairment is associated with lower quality of life and limitations that, in general, are worse when lung disease is more severe [25]. Limitations in the population have been established using disability-adjusted life years (DALYs) [26]. By 2001, COPD was the 9th greatest cause of DALYs globally, accounting for 2.5% of the global burden of DALYs and 4.8% (4th greatest cause) of deaths [27].

**Exacerbations**

Acute exacerbations of COPD account for a large proportion of the disease burden and are often associated with physician visits, hospitalisations, medication prescriptions, functional decline, and mortality. Definitions of exacerbations in epidemiological or clinical studies have ranged from self-recorded patient diary cards of symptoms, to physician-charted documentation, and from outpatient treatment or medication prescribed, to hospital and ICU admissions. One of the most commonly used definitions of an exacerbation was developed by Anthonisen et al. in 1987 and consists of a triad of respiratory symptoms: increased dyspnea, sputum volume and sputum purulence [28].

Symptoms from exacerbations may remain for up to 28 days, and repeated exacerbations may have additional negative effects [29]. There are many different triggers for exacerbations, including infections, air pollution, changes in temperature, and withdrawals from medication [14, 30, 31].

**Mortality**

COPD mortality has increased in the past 30 years, while other major causes of mortality have decreased [32]. During the period 1980–2000, the most substantial change in COPD mortality in the United States was the increasing rate for women, from 20.1/100,000 in 1980 to 56.7/100,000 in 2000, compared with the more modest increase in the death rate for men, from 73.0/100,000 in 1980 to 82.6/100,000 in 2000. One of the limitations of mortality data is that many of those who died with COPD had their death attributed to another cause [33]. Progressive respiratory failure accounts for approximately one third of the COPD-related mortality, therefore factors other than progression of lung disease must play a substantial role [34].

**Comorbid disease**

The relation between COPD and other diseases and the effect that these other diseases have on COPD has become increasingly important in recent years [35, 36]. Epidemiological data indicates that...
many COPD deaths result from cardiovascular complications [11] and that cardiovascular events are increased in COPD patients [37].

Costs
COPD is a very costly disease in the United States, with medical costs in 2002 estimated at $32.1 billion [22]. Because COPD is frequently not listed as the underlying cause of death or the primary reason for hospitalisation, this may well underestimate the true cost of COPD, which is related to direct and indirect costs involving disability, absence from work, premature mortality, and carer cost. In 2005, the medical cost of COPD per patient was estimated at US $2,700–$5,900 and attributable costs of US $6,100–$6,600 [22]. Exacerbations of COPD are the greatest burden on the healthcare system in high income countries, and can amount to 40–57% of direct costs [38].

COPD progression
Defining what constitutes ‘progression’ of COPD is critically important to those trying to better understand the natural history of COPD [3]. The decline in lung function is an important predictor of morbidity and mortality [39], but this decline may not be linear [18, 40]. It is unlikely that we wake up each day with fractionally less lung function than we had the day before. It is more probable that ‘events’ may lead to an acute drop in lung function followed by only a partial recovery [41].

While historically, most study into the progression of COPD has focused on the accelerated loss of lung function in COPD patients, this may not fully capture the multidimensional aspects of the disease. In Figure 1, we present an alternative paradigm for COPD progression. This includes:

- A — incident disease, movement from a healthy state into either an ‘at risk’ category or the presence of obstructive disease in varying degrees of severity;
- B — worsening of lung function (the ‘traditional’ viewpoint of progression), the advancement from ‘at risk’ to obstruction or from less obstruction to more severe obstruction;
- C — mortality, death related in part to the presence of disease;
- D — the development of ‘restrictive’ spirometry, either de novo or in people with existing COPD, due to comorbid disease (diabetes mellitus, congestive heart failure, muscle weakness) or other factors.

This diagram shows that some people may, relatively quickly, develop moderate to severe obstruction, and that even people with relatively mild disease may die because of COPD or its complications. In addition, it highlights the importance of people who develop ‘restriction’ on their spirometry, noted by a reduction in their FVC, something frequently related to ageing, obesity, or another comorbid disease [42].

As noted above, COPD already represents a heterogeneous group of diseases and may require more individual intervention. In the 10th revision of the International Classification of Disease (ICD-10), the World Health Organisation introduced the term ‘Chronic Lower Respiratory Disease’ to include COPD, asthma, bronchiectasis and other chronic respiratory diseases [43].

It may be time, in the respiratory community, to move towards a more holistic and inclusive view of chronic respiratory disease that includes obstructive and restrictive categories, with and without reversibility. This would move us away from the current focus in some groups on what constitutes ‘obstruction’ to a broader focus on ‘respiratory disease’ [10, 44, 45].

Conclusions
Our understanding of the natural history of COPD has increased dramatically in recent years. We now know that we can alter the natural history of disease in some patients through the use of interventions such as tobacco treatment, pulmonary rehabilitation, and medication [7, 22].

But unanswered questions remain and we have considerable room for improvement. As highlighted above, we have questions as to how the disease should be best defined. While this has resulted in spirited debate in the literature, it may not be the most important area with regard to advancing our understanding of the disease. The different phenotypes of COPD, particularly with regard to differential interventions and outcomes, should receive much greater attention. Finally, a more holistic view of what comprises COPD progression, looking well beyond the traditional lung function decline paradigm, may also provide additional insights in how to better care for our patients.

References


