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PRE – COPD: Challenges and Opportunities

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Abstract

Chronic obstructive pulmonary disease (COPD) affects one-tenth of the world's population. Globally, there is huge variation in the prevalence of COPD ranging from 2.8 to 31.5%. Another area of concern is the problem of improper diagnosis, with 10–95% under-diagnosis and 5–60% over-diagnosis. According to GOLD 2021 guidelines, the risk of misdiagnosis and over-treatment of individual patients using the fixed ratio as a diagnostic criterion is limited because spirometry is the only parameter for establishing the clinical diagnosis of COPD.The additional parameters are symptoms and other risk factors. The major concern with GOLD criteria is that the use of 70% as a fixed cut-off for forced expiratory volume in the first second (FEV1) will add a significant number of false positives compared with the use of a true lower limit of the normal. Inflammatory mediators involved in COPD include TNF-alpha and IL-6. Spirometry could be used to diagnose early COPD, but the diagnosis needs sequential measures. A meta-analysis of the available evidence for N-acetylcysteine showed that it is effective at reducing exacerbations, but the benefit was greater in subjects with chronic bronchitis without a spirometric diagnosis of COPD. Pre-COPD, although not a completely novel concept, remains poorly explored. Several potential tools for detection of pre- COPD are available like screening spirometry, sequential spirometry, impulse oscillometry and parametric response mapping. There is a clear deficiency in literature regarding treatment of early COPD. The available treatment options include inhaled bronchodilator therapy, N-acetylcysteine, vaccination and pulmonary rehabilitation. Since no current pharmacological treatment is known to halt or reverse the progression of established COPD, it is essential for the disease to be diagnosed early.

Abbreviations

WHO: World Health Organisation.

GOLD: The Global Initiative for Obstructive Lung Disease.

Pre- COPD: Challenges and opportunities.

FEV1: Forced Expiratory Volume in first second.

FVC: Forced Vital Capacity.

DLCO: Diffusing capacity of the Lungs for Carbon Monoxide.

PRM: Parametric Response Mapping.

Introduction

Chronic obstructive pulmonary disease (COPD) affects one-tenth of the world's population. According to WHO, COPD will become the third leading cause of death within 10 years. In spite of the hectic research activities, there have been no recent major strides in terms of disease modifying treatment for COPD. So far, smoking cessation remains the only intervention known to alter disease progression and improve mortality. Early diagnosis and intervention may allow a targeted approach to the instigating disease process and hence prevent progression of the disease.[1]

Prevalence of COPD

Globally, there is huge variation in the prevalence of COPD ranging from 2.8 to 31.5%. Another area of concern is the problem of improper diagnosis, with 10–95% under-diagnosis and 5–60% over-diagnosis. This is often due to differences in the definition of diagnosis of COPD across different regions and the unavailability of spirometry in many parts of low- and middle-income countries. In these areas, prevalence of COPD is also likely to be high.[1]

Levels of intervention in COPD:

1. Primary prevention with reduction of risk factors.
2. Secondary prevention with early detection and monitoring of COPD.
3. Tertiary prevention to improve health status, decrease disease progression and reduce the rate of exacerbation.

Criteria for diagnosis of GOLD grade 0 included chronic symptoms, exposure to risk factors and normal spirometry. The augmentation factor of a separate class of GOLD GRADE 0 was that the older adults with borderline abnormal spirometry have an increased risk of death and hospitalisations related to COPD. But only a minority of adults with borderline abnormal spirometry will develop COPD in their lifetime, regardless of their smoking status. Hence this grade was later discarded [2].

According to GOLD 2021 guidelines, the risk of misdiagnosis and over-treatment of individual patients using the fixed ratio as a diagnostic criterion is limited because spirometry is the only parameter for establishing the clinical diagnosis of COPD.The additional parameters are symptoms and other risk factors. Thus, GOLD favours the use of the fixed ratio over LLN.

Arguments against GOLD

The major concern with GOLD criteria is that the use of 70% as a fixed cut-off for forced expiratory volume in the first second (FEV1) will add a significant number of false positives compared with the use of a true lower limit of the normal. The fixed diagnostic cut-off ratio of 0.7, which defines current diagnosis, leads to under-diagnosis of COPD in younger individuals and over-diagnosis in older individuals. Various phenotypes of COPD might have varying natural histories.

Mannino et al argues that this false positive rate is acceptable because they found that these false positive subjects had an increased hazard of death when compared with those with FEV1 of 70%. This finding was predictable since a group with low level of lung function is being compared with a group with better lung function, even though both groups are within the normal range. Whether it is justifiable to label an asymptomatic individual with a disease on the basis of spirometric parameters that are within the accepted normal range just because they have an increased risk of death is debatable. If this argument is further developed, then male gender is also a disease since life expectancy in men is lower than in women [3].

Patients develop symptoms prior to development of airflow obstruction. The conventionally described forced expiratory volume in first second (FEV1)/ forced vital capacity (FVC) less than 0.7 could be insensitive to early airway disease. This group demonstrated that respiratory symptoms were reported by 50% of current and former smokers with preserved pulmonary function. In addition, symptomatic patients, even with preserved spirometry, had reduced exercise capacity [4].

Development of early COPD

At present, little is known about when the earliest changes of COPD begin in susceptible individuals. Several authors suggest that these changes may begin as early as in utero, progressing during childhood, for example with recurrent infections, exposure to passive smoke, etc and continue into adolescence, with further active and passive exposure to cigarette smoke resulting in a reduction in the peak attained lung function, which subsequently increases risk of being diagnosed with COPD in later life [5].

Pathogenesis

Airway inflammation first occurs during the early stages of COPD and is the key to the patho physiology and symptoms of the disease. This is because the lung inflammation contributes to airflow limitation and hyperinflation which in turn cause breathlessness on exertion and more frequent exacerbations. While inflammation in asthma is characterized by an increase in CD4+ T cells and eosinophils, increased numbers of neutrophils and CD8+ T cells are observed in COPD. Inflammatory mediators involved in COPD include TNF-alpha and IL-6 [6].

The exacerbations of COPD are associated with significant mortality, morbidity; a reduced quality of life and an increasing reliance on social care. There have been no real advancements in routine care since the 1990s [7].

Analysis of subjects involved in the National Survey of Health and Development showed that cigarette smoking during adolescence and early adulthood modifies how early-life exposures such as childhood respiratory illnesses, social class, overcrowding and pollution levels impact on midlife FEV1.At present, risk factor modification often occurs in the context of an established diagnosis, which relies on the presence of airflow obstruction. Identification and intervention of early COPD, prior to development of

established disease, would allow for potential reversal of these early changes, through patient-centred risk reduction strategies [8].

Tantucci et al suggested that the rate of FEV1 decline is more rapid in earlier stages of COPD than in later stages, especially stage II rather than stages III and IV. Although the authors highlight a lack of information on stage I COPD. This means that the potential for halting or reversing progression of disease is best when diagnosis is made at the earliest stage of disease onset [9].

The association between low BMI and poor survival among patients with COPD could be several reasons such as diaphragmatic muscle weakness, decreased lung function, and systemic inflammation, all of which is related to weight loss. Furthermore, proinflammatory status reflected by acute-phase proteins, tumour necrosis factor-a receptors, and soluble adhesion molecules is related to increasing resting energy expenditure in patients with COPD. However, loss of skeletal muscle mass is the main cause of weight loss in COPD, whereas loss of fat mass contributes to a lesser extent. In conclusion, this systematic review of 22 studies showed that for patients with COPD being overweight or obese had a protective effect against mortality [10].

Potential tools for detection of pre- COPD

GOLD advocates active case finding i.e., performing spirometry in patients with symptoms and/or risk factors. Systematic active case-finding in a primary care setting via mail-out of a screening questionnaire was also found to be an effective way to identify undiagnosed COPD patients.

Imaging in early COPD

Three features, namely, emphysema, air trapping and bronchial wall thickening, can be assessed in the identification of COPD. Comparison of inspiratory and expiratory scans can identify air trapping, and this has been utilised as a surrogate marker of small airways disease present in early disease.

Screening spirometry

The role of screening spirometry in the general population is controversial. In asymptomatic individuals without any significant exposures to tobacco or other noxious stimuli, screening spirometry is probably not indicated. Whereas in those with symptoms or risk factors (e.g.,>20 pack-years of smoking or recurrent

chest infections), the diagnostic yield for COPD is relatively high and spirometry should be considered as a method for early case finding.

Sequential spirometry

Spirometry could be used to diagnose early COPD, but the diagnosis needs sequential measures. One test, for example, can define so-called mild COPD, but whether the disease is newly incident or has been present for many years might be difficult to establish. Longitudinal use of spirometry therefore is needed to diagnose the early disease. The disadvantage of spirometry is that it is unsuitable for characterising and quantifying the underlying pulmonary pathology of COPD, including alveolar destruction (emphysema) and airway remodelling (large- and small-airway disease).

DLCO

Harvey et al. monitored a cohort of smokers with normal spirometry for 4 years and found that among those with a low DLCO (<80% predicted), 10 out of 46 patients (22%) developed obstruction on spirometry (FEV1/FVC < 0.7), whereas among those with normal DLCO, only 2 out of 59 (3%) developed obstruction, suggesting that DLCO has the ability to diagnose COPD prior to development of airflow obstruction [10].

Forced oscillometry techniques -impulse oscillometry (IOS)

Small airways have been proposed as the site of earliest changes in COPD. Oscillometry techniques allow assessment of these changes. Resistance at 20 Hz (R20) represents proximal resistance, whereas the resistance at 5 Hz (R5) represents total airway resistance. R5-20 can therefore be employed as a useful measure of small airways resistance. Frantz et al. studied subjects with and without symptoms of COPD against GOLD criteria and reported abnormal IOS findings in subjects with symptoms but normal spirometry.The authors suggest that impulse oscillometry is a potentially useful tool to diagnose early COPD prior to development of spirometric impairment [11].

The small conducting airways are the major site of airflow obstruction in COPD and may precede emphysema development. Bhatt et al. hypothesized a novel CT biomarker of small airways disease which predicts FEV1 decline. Both CT assessed functional small airways disease and emphysema are associated

with FEV1 decline, but the association with functional small airways disease has greatest importance in mild-to-moderate stage COPD where the rate of FEV1 decline is the greatest.

PRM (parametric response mapping)

A computed tomography (CT) based biomarker for monitoring regional disease progression in chronic obstructive pulmonary disease (COPD) patients, linking expiratory and inspiratory based CT metrics over time which compares quantification of emphysema on inspiratory scans to that of gas trapping on expiratory scans [12].

Galban et al., using parametric response mapping (PRM) techniques, demonstrated that functional small airways disease (fSAD) precedes the development of emphysema. Hence novel approaches to explore origins of disease are emerging, but methods to diagnose small airways disease are not standardised till now. COPD Gene cohort, which included subjects with normal spirometry but features of chronic bronchitis. Every additional 5% of lung affected by fSAD was associated with an additional FEV1 decline of 2.2 ml/year. This suggests that PRM has potential in early identification of subjects with risk of developing spirometry-defined airflow obstruction [13].

Treatment of early COPD

Inhaled bronchodilator and steroid therapy

Most literatures on treatment for COPD has focused on established disease, and there is a clear deficiency in literature on studies involving early COPD.The magnitude of clinical benefit of inhaled therapy in early COPD is limited. Although there is some evidence that bronchodilator therapy offers symptomatic benefit and reduction in exacerbation rates, long-term outcomes such as lung function decline and mortality appear unaffected.

Vaccination and pulmonary rehabilitation

There are no studies reporting specifically on the benefit of vaccination in patients with early COPD.The is currently not enough capacity to deliver conventional pulmonary rehabilitation for large numbers of patients with early disease. New modes of exercise and fitness levels such as digital interventions will need to be tested in the context of these patient groups.

N-acetylcysteine

A meta-analysis of the available evidence for N-acetylcysteine showed that it is effective at reducing exacerbations, but the benefit was greater in subjects with chronic bronchitis without a spirometric diagnosis of COPD. As chronic bronchitis often precedes development of spirometric diagnosis of COPD, it is plausible that this may provide another therapeutic avenue in patients with early COPD.

Conclusion

Pre- COPD, although not a completely novel concept, remains poorly explored. Since no current pharmacological treatment is known to halt or reverse the progression of established COPD, it is essential for the disease to be diagnosed early. A universally accepted definition of early COPD is essential to identify the pathology of early COPD.CT scan might be the new biomarker for the early diagnosis of COPD. Biomarkers are likely to play a key role in early identification and initiation of targeted therapy [14].

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