Brief Communication

Chronic Obstructive Pulmonary Disease (COPD) in Non-Smokers: A Different Phenotype?

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ABBRIVATIONS USED IN THIS ARTICLE

COPD = Chronic obstructive pulmonary disease

WHO = World Health Organization

ETS = Environmental tobacco smoke

OAD = Obstructive airway disease

ACO = Asthma-COPD overlap

Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous and multi-systemic disease with significantly increasing morbidity and mortality. COPD is now widely accepted to have multiple phenotypes. Tobacco smoking is very well recognised risk factor of COPD (25%–45% of patients with COPD have never smoked) and the burden of non-smoker COPD is increasing. This paper review in brief COPD in non-smokers, identification of various non-smoking risk factors that have contributed immensely in the causation of COPD and phenotypic variations which includes the existing and emerging phenotypes. It will also help us in proper diagnosis and pharmacological management of non-smoker COPD patients as their prevalence has been under-estimated.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles and gases. COPD is one of the leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing.[1] According to World Health Organization (WHO) estimates, more than 328 million people have COPD worldwide wherein 65 million people have moderate to severe COPD. More than three million people died of COPD in 2015, which corresponds to 5% of all deaths globally. Estimates show that COPD will become the third leading cause of death worldwide in 2030.[2,3] It is estimated that 55.3 million people have COPD and is the second leading cause of death in India as per the study published in *The Lancet Global Health* 2018.[4] Among the major causes of COPD, the role of tobacco smoking is well recognised. However, in the past decade a number of studies have suggested other important risk factors to be strongly associated with COPD. These factors include: indoor air pollution, like smoke from biomass fuel (wood, charcoal, crops, twigs, dried

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grass and cow dung), smoke from coal, mosquito coils, *agarbatti* and liquidators. Occupational exposures, such as crop farming, grain dust, organic dust, inorganic dust, coal mining, hard rock mining, brick/concrete manufacturing and gold mining, chemical exposures, like plastic and textile industries, treated pulmonary tuberculosis, lower respiratory tract infections during childhood, bronchial asthma, deviated nasal septum, outdoor air pollution, environmental tobacco smoke (passive smoking), lower socio-economic status and genetic factors.[4] There has been a lack of focus on COPD in non-smokers, despite an increase in the prevalence as per the available data provided by numerous studies published.[5-10] The present write-up aims to focus over COPD in non-smokers as different phenotypes.

Chronic obstructive pulmonary disease in non-smokers have been the topic of discussion in the recent past. There has been a lack of focus on non-smokers, specifically because of the recognition of more common and main cause of COPD, *i.e.* tobacco smoking, but emerging evidence suggests that other risk factors are equally important, especially in the developing countries. An estimated 25% to 45% of patients with COPD have never smoked; therefore, the burden of non-smoking COPD is much higher than previously believed. About 3 billion people worldwide are exposed to smoke from biomass fuel compared with 1.01 billion people who smoke tobacco, which suggests that exposure to biomass smoke might be the biggest risk factor for COPD globally.[4] Chronic cor-pulmonale due to chronic lung disease, particularly COPD, was described in non-smoker women, possibly for the first time over half of a Century ago.[5] In the last few years, the disease is described in non-smokers with an increasing incidence and there are several studies on non-smoker COPD.[5-10] This can be attributed to several emerging risk factors those has gained attention in its association and causation of COPD.

Both indoor and outdoor air pollution have been recognised as an established cause of COPD in non-smokers through exposure to noxious smoke from the combustion of biomass and solid fuels. Indoor air pollutants, such as exposure to biomass fuel, is the most commonly reported risk factor in non-smokers.[4] However, other indoor air pollutants, such as incense sticks (*agarbatti*), mosquito coils and liquidators are emerging as risk factors in non-smokers. The pollutants that are released from burning incense sticks causes airway inflammation. These sticks contain sulfur dioxide, carbon monoxide, oxides of nitrogen and formaldehyde in particulate as well as gas form, leading to inflammatory responses, such as COPD and asthma, when regularly exposed. The amount of smoke inhaled by the lungs is the same as when exposed to cigarette smoke.[4,6]

Environmental tobacco smoke (ETS) also called second-hand smoke or passive smoking, usually refers to cigarette smoke in the environment of a non-smoker. Hagstad *et al*[7] in a study at Sweden, evaluated the role of exposure to passive smoking as a potential risk factor of COPD in non-smokers. They concluded that ETS was independently associated with COPD and the association was stronger for ETS in multiple settings. ETS in multiple settings was, after age, the strongest risk factor for COPD and comparable to personal smoking of up to 14 cigarettes/day in comparable materials.[7]

Treated pulmonary tuberculosis have come out to be an emerging important risk factor which needs more emphasis in the developing countries, like India, where there is high burden of tuberculosis. In an earlier study on tuberculosis associated obstructive airway disease (OAD) was conducted to determine the association and prevalence of OAD in patients with past history of pulmonary tuberculosis in the absence of risk factor of OAD and reported a prevalence of OAD of 44.6%. Based on spirometry, no patient had mild COPD, 62% with moderate disease, 28% with severe and 10% with very severe disease.[8] Other risk factors include poorly controlled chronic asthma, occupational exposures to dusts and smokes, poor socio-economic status, deviated nasal septum[9], malnutrition and childhood respiratory infections.

Phenotypes of COPD

The term phenotype in the field of COPD is defined as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes". Amongst all phenotypes described, there are three major phenotypes that are concomitant with a different response to currently available therapies. These are: the exacerbator, the asthma-COPD overlap (ACO) and the emphysema-hyperinflation. The exacerbator is characterised by the presence of, atleast, two exacerbations the previous year, and on top of long-acting bronchodilators, may additionally require the use of anti-inflammatory drugs. The overlap phenotype presents symptoms of increased variability of airflow and incompletely reversible airflow obstruction. Due to the underlying inflammatory profile, it shows a good therapeutic response to inhaled corticosteroids in addition to bronchodilators. Lastly, the emphysema phenotype presents a poor therapeutic response to the existing anti-inflammatory drugs and long-acting bronchodilators together with rehabilitation are the only treatment of choice.[10]

In recent times, The Spanish Guidelines for COPD describes four clinical phenotypes: non-exacerbator, asthma-COPD overlap (ACO), frequent exacerbator with emphysema, and exacerbator with chronic bronchitis.[11] However, newer phenotypic variants of COPD has been classified few of which are described in table 1.

Table 1. Emerging COPD phenotypes and its definition.

COPD Phenotype	Definition
Rare exacerbators	Presence of rare exacerbations (no or just one exacerbation)
Pulmonary cachexia phenotype	Body mass index lower than 21Kg/m^2
Overlap COPD and bronchiectasis	HRCT confirmation of bronchiectasis and definite COPD diagnosis
Upper lobe-predominant emphysema phenotype	CT findings consistent to predominant upper lobe emphysema
Fast decliner phenotype	Rapid decline of lung function
Comorbidities or systemic phenotype	High comorbidities burden, predominantly cardiovascular and metabolic
α1-antitrypsin deficiency	Genetic condition caused by deficiency of α1-antitrypsin
No smoking COPD	Caused by biomass fuel exposure, other non-smoking risk factors

Phenotypical approach to COPD is having a huge impact on everyday practice and has changed non-pharmacological and pharmacological management of COPD in last decade.[12]

Non-smoking COPD Phenotype

It is a matter of great discussion and debate whether COPD in non-smokers have comparable or different pathophysiological and/or clinical characteristics than COPD in smokers. The similarities and differences in clinical presentation between smokers and non-smokers are not fully described in patients with COPD. Theoretically, the differences are expected to have diagnostic, therapeutic and prognostic importance in the near future. Fewer studies have compared the clinical features and other relevant parameters among smokers *versus* non-smoker COPD patients. A retrospective observational study concluded that non-smokers with COPD had less impairment in airflow limitation and gas exchange, and a lower prevalence of emphysema, chronic cough, and sputum compared with smokers.[13]

Histopathologically, airways of patients with COPD due to biomass fuel smoke shows more significant changes of bronchitis and fibrosis, increased eosinophilic component, anthracotic pigment deposition, thickening of airway walls and vascular endothelium.[14-16] Non-smoker COPD patients were more commonly women who predominantly presented with symptoms of chronic bronchitis.[16] A Tunisian population-based study reports significantly more symptoms and co-morbid conditions in COPD in non-smokers.[17]

The absence of a history of smoking makes it rather problematic to diagnose COPD and to distinguish from chronic asthma or ACO phenotype. There is no exact description of radiological features and of lung functions tests which are important in the overall diagnosis and disease management. One can assume the lungs to be more emphysematous with bullae formation in smokers, while non-smoker COPD patients are expected to show dominant picture of 'dirty lung fields' due to thickened and increased airway walls. Similarly, the lung function tests in non-smokers showed significantly lower values of forced vital capacity and forced expiratory volume in one second, but there were no such differences in percent predicted vital capacity, total lung capacity, partial pressure of oxygen and carbon dioxide or the dyspnoea scores.[14]

Till date, there are no differences in the pharmacological management of COPD in non-smokers from the standard care of COPD in smokers. However, different patients have different responses to treatment with bronchodilators, corticosteroids, antibiotics and other supportive drugs. Therefore, exact identification of various non-smoking risk factors needs to be studied with identification of the phenotypical variation present, which in return, would help in the proper diagnosis and more personalised management of the non-smoking COPD patients in near future.

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