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Chronic obstructive pulmonary disease in non-smokers - Is it a different phenotype?

Globally, chronic obstructive pulmonary disease (COPD) is one of the most important non-communicable diseases (NCDs) with a progressive downhill course[1,2]. It is a major cause of global healthcare burden, including in India[2-5]. COPD is one of the few NCDs whose prevalence continues to rise in spite of the vastly expanded drug formulary. Population prevalence has been variously reported from different regions depending on the local prevalence of various risk factors[3]. In India, an average prevalence of 3.5 per cent was reported in a large population study (INSEARCH) undertaken at 16 different centres in the country[6]. Similar figures were reported in other studies[7,8]. Tobacco smoking has been the most common cause of COPD as described in innumerable reports including a few from India[9,10].

Chronic obstructive pulmonary disease (COPD) in non-smokers

COPD has also been described in non-smokers with a variable frequency[9,10]. There has been a lack of focus on the non-smokers, especially because of the recognition of more common and important cause of COPD *i.e.*, tobacco smoking. Chronic cor pulmonale due to chronic lung disease (conceptually COPD) was described in non-smoker women, possibly for the first time in non-smokers, over half of a century ago[11]. In the last few years, the disease is described in non-smokers with an increasing frequency and there are several reports on non-smoker COPD[6,7,12-14]. This can be partly attributed to an increased concern about air pollution.

Both indoor and outdoor air pollutions are recognized as a cause of COPD through exposure to smoke from combustion of solid or biomass fuels. Household air pollution is the most frequently reported risk factor in non-smoking population[11-16]. The extent of air pollution is also influenced by seasonal and diurnal variations, climatic conditions and rains. Exposure to non-fuel-related air pollutants such as environmental tobacco smoke (*i.e.*, passive smoking), volatile gases, fumes and dusts, industrial and traffic exhausts may also contribute to the development of COPD[12-16]. Other risk factors include poorly controlled chronic asthma, occupational exposures to dusts and smokes, poor socio-economic status, malnutrition, childhood respiratory infections and old-treated pulmonary tuberculosis[12,15,16].

It is also important to precisely define an ex-smoker based on the duration of smoking-cessation and quantum of smoking. With reference to COPD phenotypes, it is debatable whether they should be classified amongst smokers, non-smokers or as a distinct category.

COPD phenotypes

COPD is a heterogeneous disease which incorporates chronic bronchitis (CB) and emphysema as the two important clinical diagnoses recognized in the past. COPD became the preferred term because of the difficulties to distinguish between the two conditions in view of a significant overlap of clinical, radiological and pathological features. With an increased understanding of COPD in the recent times, there is a distinct therapeutic advantage of recognizing the different presentations commonly referred to as clinical phenotypes. Many different clinical and pathological phenotypes have been described in general as well as in smokers - the exacerbator, the emphysema-hyperinflation and the asthma-COPD overlap (ACO) being the three most commonly recognized phenotypes[17].

The number of exacerbations constitutes the most important distinguishing criterion of clinical phenotypes. Two distinct clusters based on exacerbation frequency were reported in a study which employed receiver operating curve analysis on longitudinal cluster data; frequent exacerbators

with two moderate-to-severe exacerbations per year had more air-flow obstruction, clinical symptoms and impairment of health-related quality of life parameters[18]. The Spanish COPD Guidelines[19] describe four clinical phenotypes: (*i*) non-exacerbators, (*ii*) ACO, (*iii*) frequent exacerbators with emphysema, and (*iv*) frequent exacerbators with CB. Several differential characteristics were similarly described in frequent exacerbators of both emphysema and CB phenotypes compared to those of infrequent exacerbators[20].

Non-smoker COPD phenotype?

It remains questionable whether COPD in non-smokers has similar or different pathophysiological and/or clinical characteristics than COPD in smokers. Similarly, COPD in ex-smokers may have different clinical and pathophysiological features because of the differential role played by multiplicity of and years of exposure to different risk factors. Conceptually, the differences are likely to have diagnostic, therapeutic and prognostic significance. There are a few reports on differences in clinical features and other parameters among smokers' versus non-smokers' COPD[21,22]. Also, non-smoking patients with COPD have predominant airway involvement compared to smokers with COPD[21,22]. It is also debatable whether an ex-smoker should be considered as a non-smoker or a separate category. In a recent study, distinct radiological and pathological differences were reported in COPD due to biomass exposure[23]. However, it remains to be seen if COPD in non-smokers is a distinct phenotype? Such an observation may have significant therapeutic and prognostic importance[24].

Histopathologically, airways of patients with COPD due to biomass fuel smoke show more significant changes of bronchitis and fibrosis, increased eosinophilic component, anthracotic pigment deposition, thickening of airway walls and vascular endothelium[25-27]. Non-smoker COPD patients were more commonly women who predominantly presented with symptoms of CB[27]. A Tunisian population-based study reports significantly more symptoms and co-morbid conditions in COPD in non-smokers[28]. On the other hand, a study from China did not support these finding[29].

Phenotypic differences are important because of the issues related to diagnosis and treatment differences in clinical practice. The absence of a history of smoking makes it somewhat difficult to diagnose COPD and to differentiate from chronic asthma or from ACO phenotype. There is no clear description of radiological features and of lung functions tests which are important in the overall diagnosis and disease management. One can expect the lungs to be more emphysematous with bullae formation in smoker patients while non-smoker COPD patients are likely to show dominant picture of 'dirty lung fields' due to thickened and increased airway walls. Similarly, the lung function tests in non-smoker patients showed significantly lower values of forced vital capacity (FVC) and FEV_1 (forced expiratory volume in one second), but there were no such differences in per cent predicted vital capacity, total lung capacity, partial pressure of oxygen and carbon dioxide (PaO_2 and $PaCO_2$) or the dyspnoea scores[25].

There are no differences in the pharmacological management of COPD in non-smokers from the standard care of COPD in smokers. It is however, known that different patients have different responses to treatment with bronchodilators, corticosteroids, antibiotics and other supportive drugs. It remains to be seen if the non-smokers as well as the ex-smokers COPD patients have more (or lesser) number of exacerbations, require differential treatment and/or respond differently than the smoker COPD patients. At present, even though the data are scarce, it is reasonable to believe that non-smoker COPD is a distinct clinical phenotype which is more akin to the CB phenotype. Further observational and investigational studies are required to answer some of these questions.

***Conflicts of Interest*:** None.

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