An Overview of Chronic Obstructive Pulmonary Disease (COPD): Epidemiology and Pathogenesis

Type of Article: Review

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is one of the most common chronic respiratory diseases which contribute significantly to the burden of non-communicable diseases. With the increasing prevalence of COPD in developing countries a good knowledge of disease burden and process is essential.

Methods: Review of the available literature on the subject was done through Medline and Google search utilising the following keywords COPD; epidemiology; pathogenesis and management.

Result: COPD which is increasing in prevalence has varied pathogenetic mechanisms which are influenced by both intrinsic and extrinsic environmental promoters.

Conclusion: The prevalence of COPD is increasing especially in developing countries.The pathogenesis is multifactorial and current understanding provides insights that are expected to improve on treatment and outcome.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. It is primarily caused by cigarette smoking. Although COPD affects the lungs; it also produces significant systemic consequences[1].

Chronic bronchitis is defined clinically as chronic productive cough on most days for three months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded[2].

Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis[3].

The chronic airflow limitation which is the hallmark of COPD is caused by small airway disease i.e. chronic obstructive bronchiolitis and destruction of lung parenchyma i.e. emphysema. The relative contribution of each of these varies between individuals. At this point it is important to note that chronic bronchitis is an epidemiological diagnosis while emphysema is a pathological diagnosis either of these conditions may or may not occur in COPD but are not necessary for the diagnosis of COPD.

Risk Factors

COPD is more like a cluster of heterogenic disorders with a common presentation (non-reversible airflow limitation) as such it does not have any single aetiology. While there are several risk factors for COPD. Cigarette smoking is the best known and most studied risk factor. Others factors include air pollution (indoor and outdoor) occupational exposure, recurrent childhood chest infections, advance age and male gender. Much of the evidence concerning

risk factors for COPD has come from cross-sectional studies which identifies associations rather than cause and effect relationships. Although some studies have followed cohorts for up to 20 years[4, 5], no study has examined the entire course of the disease as such the current understanding of the risk factors for COPD is still incomplete.

COPD results from the interaction of the environmental factors with genetically

Host factors	Exposure
Genetic	Tobacco smoking
Gender	Socio-economic factors
Airway hyper-responsiveness, immunoglobulin E and asthma	Occupation
	Environmental pollution
	Indoor air pollution
	Perinatal events and childhood illnesses
	Recurrent respiratory infections
	Diet

Host factors:

Cigarette smoking is the main risk factor for COPD but only about 15% of smokers develop clinically significant disease[6]. Previous studies estimated that smoking contributes 15% to the variability of lung function[7] while genetic factors may account for up to 40%[8] . Further argument for a genetic basis for COPD is that over the years COPD has been shown to aggregate in families[9, 10]. Several studies have shown an increased prevalence of COPD among relatives of COPD patients compared with those of controls[11, 12]. The prevalence of COPD has been shown to have an indirect relationship with genetic distance[13, 14]. However, none of these approaches provides definitive evidence for the existence of genetic risk factors for COPD.

The genetic risk factor that is best known and extensively studied is a severe hereditary deficiency of α1-antitrypsin a protease inhibitor that is secreted by the liver and pulmonary macrophages and its function is to limit the activity of extracellular proteases. α1-antitrypsin deficiency is only relevant to a small part of the world's population but it illustrates the importance of gene-environment interactions in the pathogenesis of COPD[15].

Genetically determined alterations in the activities of some other proteases and anti-proteases may also play a part in lung destruction. Some studies have found an association between polymorphysm of Alpha-1-antichymotrypsin (AACT)[16, 17], Alpha-2-macroglobulin (A2M)[18], Matrix metalloproteinases(MMPs)[19-21] and the development of lung destruction with emphysema while some other studies have found no such association[22, 23].

Genetic variation in the handling of noxious substances such as hydrocarbons, epoxides and oxidants could be important determinants of host response and the resulting tissue damage. Polymorphism of the Microsomal epoxide hydrolase (EPHX) gene with reduction in enzyme activity has been associated with severe forms of COPD[24, 25] but the results are not consistent[26]. Homozygous deletion of the Glutathione S-transferases (GSTs) gene has been associated with chronic bronchitis[27] but this finding is also not consistent[26]. Mutation in the Cytochrome P450 1A1 (CYP 1A1) gene which results to an increased activity of the enzyme has been associated with susceptibility to emphysema [28]. Other candidate genetic abnormalities which may influence the development of COPD include antioxidants such as heme oxygenase-1, pro-inflamatory mediators such as tumour necrosis factor α, interleukin-1 complex and Vitamin D-binding protein[29].

The precise role of genetic abnormalities in the development of COPD is still not clear and most of the studied genes and their products remain as plausible candidates.

Airway hyper-responsiveness has also been demonstrated to be a risk factor for COPD[30]. The mechanism for this is not quite clear but polymorphism of the β-2 adrenegic receptor has

been shown to affect bronchodilator response[31] and lung function[32]. Some asthma patients also develop fixed airflow limitation as the disease progresses and can therefore be classified as COPD[33].

Worldwide, COPD is more prevalent in males than in females. However, this may be a consequence of the marked difference in smoking and other exposures between males and females. However women are less likely to be diagnosed and treated for COPD[34-36]. Recent data from several large studies suggest that tobacco smoke may affect women more than men[37].

Exposure:
Cigarette smoking: Tobacco smoke is by far the most important risk factor for COPD worldwide[5]. Smokers are more likely to have abnormal lung function and to develop COPD[38]. This effect of cigarette smoke is not restricted to the direct smoker but also extends to the second hand smoker. Several studies have demonstrated an association between environmental tobacco smoke and COPD [39, 40].

Occupational exposure:
Data from the US**National Health and Nutrition Examination Survey** (NHANES) III survey indicate that occupation can be an important risk factor for COPD. The fraction of COPD attributable to work was estimated as 19.2% overall and 31.1% in never-smokers[41].

Socioeconomics: A subject's socioeconomic background plays an important role that is beyond the effects of exposure to tobacco and occupational hazards[42]. It is increasingly apparent that COPD often has its roots decades before the onset of symptoms. Impaired growth of lung function during childhood and adolescence, caused by recurrent infections or tobacco smoking, may lead to lower maximally attained lung function in early adulthood[43]. Whether the effect is due to impaired growth of lungs and airways or an increased rate of infection is not clear.

Indoor air pollution: In developing countries, indoor air pollution, due to the use of biomass fuels for heating and cooking, may pose a significant particulate burden and contribute to COPD, especially in females[44]. Often, the stoves being used have poor combustion capacity and can utilize only a fraction of available fuel energy. As a result of the poor combustion, these stoves produce heavy smoke and release a number of harmful pollutants. This situation is compounded by poor ventilation in the cooking areas[45].

Respiratory infections: One factor that has recently received closer attention is the presence of lower respiratory infection during childhood and this has been shown to be associated with an increased risk of respiratory symptoms[46], obstructive airway disease[47], and functional impairment[49].

Acute respiratory infections in childhood are not the only type of infections implicated in the development of COPD. Tuberculosis (TB) and COPD share similar respiratory symptoms such as chronic cough, weight loss and shortness of breath. They also share risk factors such as cigarette smoking[49, 50] and low socio-economic status. The effects of HIV infection on TB are well known[51], however HIV infection is increasingly being recognised as a cause of premature emphysema which occurs with fewer pack-years[52, 53]. As far back as the 1800s, Laennec had documented the association between TB and obstructive airway disease[54]. This association is receiving more attention of late. In a survey to determine the prevalence and predictors of chronic bronchitis in South Africa, the authors found that a previous history of pulmonary TB was the strongest predictor of chronic bronchitis; OR 4.9; 95% CI 2.6–9.2 for the men and OR 6.6; 95%CI 3.7–11.9 for the women[55]. Studies from Latin America[56] and South East Asia[57] have reported similar findings. The association between TB and chronic airway obstruction shows an inverse relationship between the lung function and extent of lung involvement[58] as well as with frequency of infection[59].

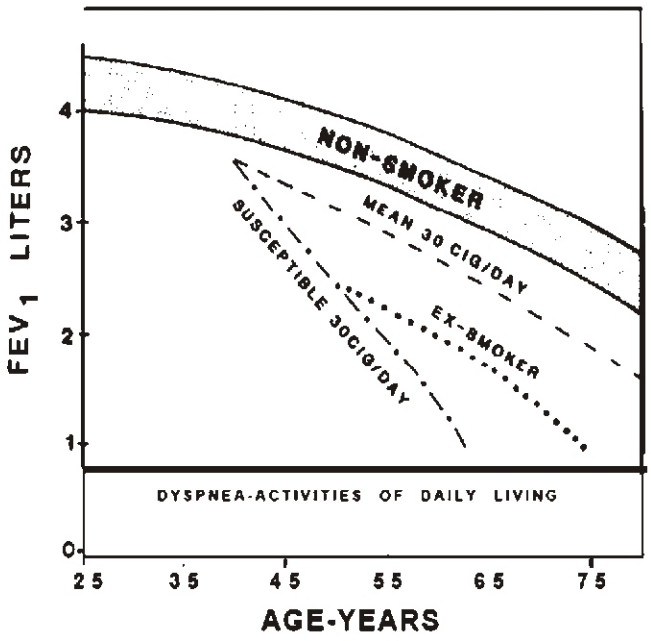
Epidemiology
Despite the fact that COPD is now prevalent in

both developed and developing countries, reliable estimates of its prevalence are surprisingly scant in most parts of the world. However, population-based estimates of the disease prevalence by region is problematic since the disease is progressive, measurement tools and definitions still vary among studies, and implementation of spirometry on such a scale is often not feasible in developing regions. The Burden of Obstructive Lung Disease (BOLD) initiative was an attempt to accurately measure the worldwide prevalence of COPD and its risk factors in adults aged 40 years and older and to investigate variation in prevalence across countries by age, sex, and smoking status using standardised methods[60]. The investigators recruited 9425 participants from 12 sites. They observed that the prevalence of COPD that was stage I or higher varied significantly across sites ($p<0{\cdot}0001$) and was generally greater in men than in women. The prevalence of stage II or higher COPD was 10·1% (SE 4·8) overall, 11·8% (7·9) for men, and 8·5% (5·8) for women and varied from site to site such that stage II COPD in women ranged from 5·1% in Guangzhou, China, to 16·7% in Cape Town, South Africa, and in men it ranged from 8·5% in Reykjavik, Iceland, to 22·2% in Cape Town, South Africa. Generally, the prevalence of COPD that is stage II or higher increased steadily with age for men and women in every site[61].

In the Global Burden of Disease Study (GBD), it was estimated that 63.6 million people have symptomatic COPD in 2008 and COPD will be responsible for three million deaths worldwide[62]. The prevalence of COPD was estimated to be highest in the Western Pacific which includes China and India and lowest in Africa. The low prevalence of COPD in Africa may be a reflection of Africa's young population, with more than 40% under 15 years and only 3.2% over 65 years, as well as the low prevalence of smoking.

In Africa, most of the prevalence surveys on chronic bronchitis have been conducted in limited and specific population groups. These studies often use the British Medical Research Council questionnaire[63] to determine the prevalence of chronic bronchitis. In a survey for the prevalence of chronic bronchitis in South Africa by Erhlich et.al found a prevalence of 2.3% among men and 2.8% among women[55]. In Nigeria few community based studies have been carried out. Desalu et.al in a study to determine the prevalence and risk factors for chronic bronchitis among rural women in South West Nigeria, recorded a prevalence of chronic bronchitis of 10.6% among women in who cook with fire wood compared to 2.8% for women who do not[64].

Figure1: Relationship of FEV1, age, and smoking[68]



Non-smokers lose FEV1 at an accelerating rate with age; the average loss is about 30 ml/yr. Smokers of 30 cigarettes per day average a slightly greater rate of decline and have FEVl values slightly below average when first studied at age 40yr. A small proportion of susceptible smokers (about 15%) lose function much more rapidly, approximately 150 ml/yr, with FEV1 of 0.8 L by age 65, a level so low that they experience dyspnea in the course of ordinary daily living. Susceptible smokers who stop smoking at age 50 do not regain lost function or regain only a little, but they subsequently lose function at the same rate as never-smokers; dyspnea with ordinary activity will not develop until the mid-seventies[68].

Pathology of COPD

COPD comprises major pathological changes in

the central airways, peripheral airways, lung parenchyma and pulmonary vasculature.
Bronchial glands hypertrophy with goblet cell metaplasia occurs in the central airways[69]. This results in excessive production of mucous. Cellular infiltrates also occur in bronchial glands. Squamous metaplasia of the airway epithelium occurs with loss of cilia and ciliary dysfunction. There is also increased smooth muscle and connective tissue deposition[70]. In the airways wall lymphocytes, predominantly of the CD8+ type predominate. As COPD progresses neutrophils also become prominent[71]. In the airspaces, in addition to lymphocytes, neutrophils and macrophages can also be identified[72].

Bronchiolitis is present in the peripheral airways early in the disease[73]. There is pathological extension of goblet cells expansion and squamous metaplasia into the small airways[74]. The inflammatory cells in the airway wall and airspaces are similar to those in the central airways[75]. As the disease progresses, there is increasing fibrosis in the airway walls[76].

The pathology of the lung parenchyma is characterised by emphysema. There is a significant loss of alveolar attachments, which contributes to peripheral airway collapse[77]. Two types of emphysema occur; centrolobular and panlobular emphysema. centrolobular is the most common type of emphysema in COPD and the lesion predominates in the upper zones. Panlobular emphysema is prominent in patients with α1-antitrypsin deficiency and predominates in the lower zones. Early in the disease, they are microscopic lesions but as the disease progresses they may become macroscopic or form bullae. The cellular infiltrates are similar to that of the airways[78].

Early changes in pulmonary vessels consists of , thickening of the vessel wall and endothelial dysfunction[79] followed by increased vascular smooth muscle and infiltration by inflammatory cells[80] In advanced stages of the disease, there is fibrosis and emphysematous destruction of the capillary bed[81] Ultimately, these changes lead to pulmonary hypertension and right ventricular dysfunction[82].

Pathogenesis

Tobacco smoking is the main risk factor for COPD, although other inhaled noxious particles and gases also contribute to the development of COPD. This causes an exaggerated inflammatory response in the lungs of susceptible people, which eventually causes tissue destruction. Two other processes that are also important in the pathogenesis of COPD are an imbalance of proteinases and anti-proteinases in the lungs, and oxidative stress.
COPD is characterised by an increase in neutrophils, macrophages and CD8+ T-lymphocytes in the lung parenchyma and airway. There may be an increase in eosinophils in some patients, particularly during exacerbations[83]. These inflammatory cells are capable of releasing a variety of cytokines and inflammatory mediators, most notably leukotriene-4, interleukin-8 and tumour necrosis factor-α. This inflammatory pattern is markedly different from that seen in patients with bronchial asthma.

An imbalance in proteinase / anti-proteinase activity may occur in COPD due to increased production or activity of proteinases or inactivation or reduced production of anti-proteinases. Cigarette smoke and possibly other COPD risk factors, as well as inducing inflammation, can produce oxidative stress that, induces inflammatory cells to release proteinases and also decreases or inactivates several anti-proteinases by oxidation. These Proteinases are also inducer of mucous secretion and mucous gland hyperplasia[84,85].

Oxidative stress triggered by smoking and or inhalation of pollutants can contribute to COPD by oxidising a variety of biological molecules, damaging the extracellular matrix, inactivating key antioxidant defences or enhancing gene expression either by activating transcription factors or promoting histone acetylation[86]. Different markers of oxidative stress are found in increased amounts in the lungs, exhaled air breath and urine of smokers and patients with COPD. They include hydrogen peroxide, nitric

oxide and lipid peroxidation products[87].

Pathophysiology

The physiological abnormalities in COPD include: mucous hypersecretion and cilliary dysfunction, airflow limitation and hyperinflation, gas exchange abnormalities, pulmonary hypertension, and systemic effects.

Mucous hypersecretion and cilliary dysfunction are typically the first physiological abnormalities in COPD. The former is due to stimulated secretion from enlarged mucous glands. The latter due to squamous metaplasia of epithelial cells. Expiratory airflow limitation is the physiological hallmark of COPD. The major site of this airflow limitation is in the smaller conducting airways less than 2 mm in diameter and is mainly due to airway remodelling, loss of elastic recoil and destruction of alveolar support, smooth muscle contraction and mucus hyper-secretion[88]. Dynamic hyper-inflation is one of the major contributors to exercise limitation in these patient[89]. Gas exchange abnormalities occurs in advanced disease and are characterised by arterial hypoxaemia with or without hypercapnia. The main mechanism of abnormal gas exchange in COPD is the distorted lung architecture[90]. Pulmonary hypertension usually occurs after the development of severe gas exchange abnormalities. Factors contributing to pulmonary hypertension in COPD include hypoxic vasoconstriction, endothelial dysfunction, remodelling of pulmonary arteries and destruction of the pulmonary capillary bed. This may eventually lead to right ventricular hypertrophy and dysfunction[91].

Systemic effects of COPD which includes systemic inflammation and skeletal muscle wasting, contribute to limit the exercise capacity of these patients and to worsen prognosis, independent of their pulmonary function[92].

CONCLUSION

In summary airflow limitation in COPD is caused by obstructive bronchiolitis and emphysema. COPD occurs in genetically predisposed individuals; the exact nature of this predisposition is not very clear but A1Antitrypsin deficiency is the best known genetic disorder associated with COPD. Smoking may be the most studied risk factor for COPD but among patients in developing countries, other factors such as indoor air pollution, childhood illnesses and previous tuberculosis infection trump cigarette smoking in importance. For patients who are predisposed to COPD, it is characterised by an accelerated decline in lung function which goes unnoticed until the FEV1 falls below the threshold and the patient then develops symptoms. Accurate worldwide data do not exist for COPD due largely to differences in definition. The BOLD study demonstrated that COPD prevalence increased with age but varied widely between regions.

The pathology of COPD is characterised changes in airways, lung parenchyma and blood vessels of the lungs triggered by chronic inflammation with CD+8 lymphocytes, neutrophils and macrophages. The inflammatory process also activates proteinases, deactivates anti-proteinases and causes oxidative stress all leading to tissue damage. These changes in the lungs lead to altered function characterised by excessive mucus production, cilliary dysfunction, airflow limitations, gas exchange abnormalities, pulmonary hypertension and systemic effects such as wasting.

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