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Review Article

Chronic Obstructive Pulmonary Disease: A Challenge to the Healthcare System

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ABSTRACT
Chronic obstructive pulmonary disease (COPD) is an umbrella term which includes chronic bronchitis and emphysema coexisting in the lungs of large number of patients. It is the fourth leading cause of death worldwide. The important risk factors for COPD take account of genetic factors, tobacco smoke, exposure to indoor and outdoor air pollution, occupational hazards, various infections etc. Significant pathological changes that take place in the lungs of patients can be characterized by an excess of extracellular matrix deposition, increased thickness of airway walls, mucus hypersecretions and destruction of alveolar septae. Both pharmacological and non-pharmacological treatment strategies are currently employed to manage this diesease. Future advancements and innovations in this avenue at molecular level and development of new drug therapies will surely lead to improved therapeutic interventions. This manuscript highlights various clinical manifestations, diagnosis and treatment strategies of this severe disease.

Keywords: COPD, Emphysema, Treatment Strategies.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a group of disorders characterized by chronic airflow obstruction and limitation [1]. It is a major cause of health care burden worldwide and leading cause of death [2]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), it is defined as a disease state characterized by airflow limitation that is not fully reversible. It includes *emphysema*, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli, *chronic bronchitis* which is a condition with chronic and recurrent mucus secretion and *small airways disease*, a condition in which small bronchioles are narrowed [3]. COPD patients can be identified on the basis of smoking history, respiratory symptoms and spirometric measurements of lung function [4]. Figure 1 represents the clinical manifestations of COPD. It depicts the main cause related to airflow limitation is peripheral airway lesion. There are various instances in which primarily destruction of the alveolar system lead to conditions favoring emphysema. In some cases, primarily progression of central airway lesion leads to a preponderance of airway lesions. The concept of COPD encompasses various alveolar-peripheral airway-central airway lesions [5].

Different Stages of COPD: Disease severity is classified into various stages based on spirometric classification as shown in table 1. Spirometry is essential for diagnosis and provides a useful description of the severity of pathologic changes in COPD. Various stages include:

FEV_1: Forced expiratory volume, FVC: Forced vital capacity

Risk Factors: Risk factors for COPD include both host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors. Host factor which is best documented is a rare hereditary deficiency of α_1-antitrypsin. The major environmental factors are tobacco smoke, heavy exposure to occupational dusts and chemicals (vapors, irritants and fumes); and indoor/outdoor air pollution [6].

Genetic Factors: The best known factor linked to COPD is a deficiency of the serine protease α_1 antitrypsin, which arises in 1-3% of patients with COPD. Having low concentrations of this enzyme, particularly in combination with smoking or other exposures, increases the risk of panlobular emphysema [8].

Tobacco smoke: Worldwide, tobacco smoke remains the most important cause of COPD [9]. Cigarette smokers have higher prevalence of lung-function abnormalities and respiratory symptoms [6]. WHO estimates that in high-income countries, 73% of COPD mortality is related to smoking [9]. Furthermore, smoking during pregnancy can negatively affect fetal lung growth and result in development of lung disease [10].

Occupational dust, vapors and fumes: Occupational exposures include organic and inorganic dusts, chemical agents and fumes [11]. Exposure to various dusts, chemicals, vapors and fumes in the work place is a factor for many people with COPD [12]. In countries of low and middle income, where occupational exposures to dust and fumes could be greater than in high-income nations because of less stringent laws, work exposures can

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assume high importance as a risk factor [13].

Indoor and outdoor air pollutants: High levels of urban air pollution are harmful to persons with existing heart or lung disease. The role of outdoor air pollution in causing COPD appears to be small when compared with cigarette smoking [6].

Ageing: COPD prevalence, morbidity and mortality increases with age. Lung function, which reaches its peak level in young adults, starts to decline in the third and fourth decades of life [14,15].

Infections: Infections have an important role in both development and progression of COPD [16]. A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood [17,18]. Most COPD exacerbations are related to bacterial or viral infections [16].

Socioeconomic status: Poor populations tend to have a higher risk of developing COPD and its complications than their wealthier counterparts [19-20]. There is evidence that the risk of developing COPD is inversely related to socioeconomic status [21].

Pathology: Pathological changes characterstic of COPD are found in the central airways, peripheral airways, lung parenchyma and pulmonary vasculature [22].

In the central airways- the trachea, bronchi and bronchioles greater than 2-4 millimeter in internal diameter-inflammatory cells infiltrate the surface epithelium [23,24]. Enlarged mucus-secreting glands and an increase in the number of goblet cells are associated with mucus hypersecretion. In the peripheral airways-small bronchi and bronchioles that have an internal diameter of less than 2 millimeter, chronic inflammation leads to repeated cycles of injury and repair of the airway wall [25]. Repair process results in a structural remodeling of the airway wall, with increasing collagen content and scar tissue formation that narrows the lumen and produces fixed airways obstruction [26]. Destruction of the lung parenchyma in patients with COPD typically occurs as centrilobular emphysema [27]. An imbalance of endogeneous proteinases and antiproteinases in the lung resulting from genetic factors or the action of inflammatory cells and mediators is thought to be a major mechanism behind emphysematous lung destruction [28]. Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that begins early in natural history of the disease [29].

Different pathogenic mechanisms produce the pathological changes which in turn give rise to the following physiological abnormalities in COPD: mucus hyper secretion and cilliary dysfunction; airflow limitation and hyperinflation; gas exchange abnormalities; pulmonary hypertension and systemic effects [30,31,32].

Pathophysiology: Pathologic changes in the lungs lead to corresponding physiologic changes and depict characteristics of this disease, including mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lungs capacity for gas exchange, producing hypoxemia and, later on, hypercapnia [33]. In general, gas transfer worsens as the disease progresses. Mild to moderate pulmonary hypertension may develop late in the course of COPD which is the major cardiovascular complication of COPD [7,33]. COPD is characterized by periodic episodes of worsening lung function and symptoms called as exacerbation. Some estimates suggest that at least 50% of episodes are viral. Furthermore, bacterial, viral and atypical pathogens either alone or in concert have been implicated in inducing majority of acute exacerbations [34].

Symptoms of COPD: Various symptoms of this disease are:

- Inability to take deep breath.
- Frequent sighing/erratic ventilation at rest.
- Chest tightness, malaise and fatigue.
- Decreased exercise tolerance.
- Wheezing and decreased breath sounds.
- Weight loss may be reported by the patients with primary emphysema, but the patient with chronic bronchitis is typically obese.
- Health related quality of life is also distressed [32,35,36,37,38].

Prevalence: Most of the information available on COPD prevalence, morbidity and mortality comes from developed countries [39]. In 2000, over 119,000 deaths in the United States and 2.74 million deaths worldwide were attributed to COPD. Data from the National Health Interview Survey in 2001 indicates that 12.1 million people over age 25 years in the United States have COPD. Over 9 million of these individuals have chronic bronchitis; the remaining numbers have emphysema or a combination of both diseases [32]. Study performed by the Global Burden of Disease conducted under the auspices of the World Health Organization (WHO) and World Bank concluded that the worldwide prevalence of COPD in 1990 was estimated as 9.34/1,000 and 7.33/1,000 in men and women respectively [40,41]. The prevalence of this disease is highest in those countries where cigarette smoking is very common [6]. This disease also accounted for 8 million medical outpatients visits, 1.5 million visits in emergency departments, and around 700,000 hospitalizations in the year 2000 [35]. COPD is currently the fourth leading cause of death in the united states and is expected to become third leading cause of death by 2020 [42].

Indian Scenario: COPD in India has been recognized and investigated with the help of several small surveys conducted in different populations for the last 40 years. Prevalence rates varying from about 2 to 22 % in men and from 1.2 to 19 % in women [43]. A median prevalence of 5 % in men and 2.7 % in women was calculated which accounted for a total burden of 8.15 million male and 4.21 million female patients in a population of 944.5 million in 1996 [44]. Study from

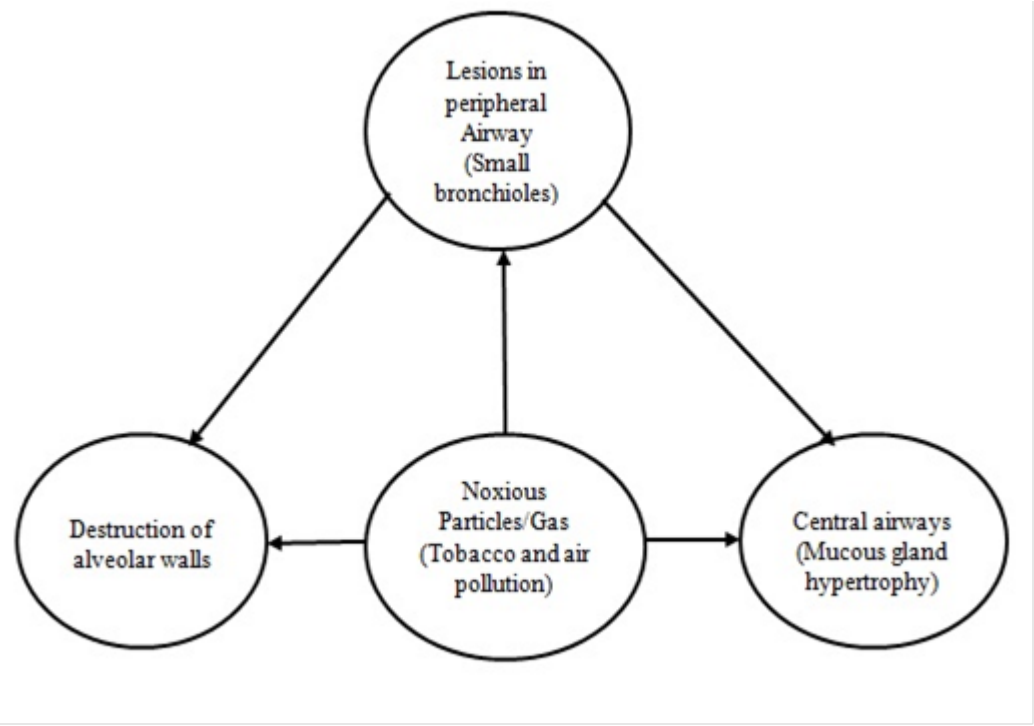

Figure 1: Clinical manifestations of COPD

urban Kashmir points to a higher prevalence of 7.55 % in smokers and 10.56 % in people living in poorly ventilated houses [45]. Although the prevalence rates reported from south India were earlier considered as lower, almost similar findings were reported in population survey on 9,946 inhabitants from rural south India i.e., a prevalence of 40.8/1000 for males and 22.5/1000 for females [46].

A multicentric study sponsored by the Indian Council of Medical Research (ICMR) is the largest and the most appropriately conducted field study on asthma and COPD which provides data on prevalence as well as on the risk factors. A field survey was conducted in both the urban and rural populations at four large centers i.e., Bangalore, Chandigarh, Delhi and Kanpur on a total sample of over 73,000 individuals. Of the 35,295 adult subjects of over 35 yr of age, COPD was diagnosed in 4.1 % individuals with a male to female ratio of 1.56 to 1 i.e., a prevalence of 5.0 % among men and 3.2 % in women [2]. Thus, COPD is more common among males than females. The male to female ratio varied from 1.32:1 to 2.6:1 with median ratio of 1.6:1 [44]. A large scale study in Hyderabad city and its surrounding municipalities, covering a population of more than 54 lacs and 28 hospitals/health posts, was done in 2001. The rates of hospital admissions of cases with COPD showed an age differential. The rate was 47.84/100,000 persons at the community level, it was 57.28 for those 18-64 years of age and 546.17 for those above 65 years of age [47].

Diagnosis: Diagnosis of COPD should be performed in any patient who has the symptoms of cough, sputum production, dyspnea and history of exposure to risk factors [37]. The diagnosis includes spirometry, reversible testing, chest X-ray, arterial blood gas test, computed tomography and pulse oximetry.

Spirometry: The presence of airflow limitation should be confirmed with spirometry. Spirometry represents a comprehensive assessment of lung volumes and capacities. It should be performed by a qualified person and according to American thoracic society criteria. Obstruction to the airflow is present when the FEV_1/FVC ratio is less than 70% [32,34].

Bronchodilator reversibility testing: It should be performed at least initially to establish a baseline, rule out other causes and estimate prognosis. A short acting bronchodilator is administered and spirometry is repeated in 15 to 30 minutes [35]. *Chest X-ray:* Chest radiography is performed on the majority of patients suspected of having chest disease. A posterior-anterior film provides information on the lung fields, heart, mediastinum, vascular structures and the thoracic cage [36].

Computed tomography: CT scanning provides detailed images of pulmonary parenchyma, mediastinum, pleura and bony structures. High resolution computed tomography and bronchoscopy are also done for direct and indirect visualization of airway anomalies and sampling of deep bronchial secretions. These tests are the key to make the diagnosis of Mounier-kuhn syndrome [36,48].

Pulse oximetry: It is useful in most patient, especially those with advanced disease (FEV_1<50%) or polycythaemia, in order to check for significant hypoxaemia [49].

Gamma scintigraphy: Diagnostic imaging using gamma scintigraphy is well established procedure in nuclear medicine and has been extensively used in inhalation drug delievery development. It is the only non-invasive method currently capable of providing human data on total and regional lung deposition and mucociliary clearance [50].

Other tests can be useful in some patients, such as more

Table 1: Various Stages of COPD Severity [3,5,6,7]

Stage	Stage 0	Stage I	Stage II	Stage III	Stage IV
Classification	At Risk	Mild	Moderate	Severe	Very Severe
Symptoms	Chronic cough, sputum production	Chronic cough and sputum production sometimes present.	Regardless of the presence or absence of chronic symptoms.	With or without chronic cough or sputum production.	Accompanied with chronic respiratory failure or right heart failure.
Ratio of FEV_1:FVC after bronchodilator	> 70%	≤ 70%	≤ 70%	≤ 70%	≤ 70%
FEV_1 % of predicted value	≥ 80%	≥ 80%	50-80%	30-50%	< 30%

extensive assessments of lung volumes through body plethymography, arterial blood gas test, carbon dioxide diffusion capacity, exercise testing and test of respiratory muscle strength [35].

Management Strategies: There are three treatment strategies for managing COPD which are summarized in the following text.

Pharmacological treatment includes the use of bronchodilators, inhaled corticosteroid, sympthomimetic, combination therapy, long term oxygen therapy, antibiotic therapy and respiratory stimulants. Non pharmacological treatment includes smoking cessation, optimizing nutrition, pulmonary rehabilitation, mechanical ventilation and breathing exercise. Surgical management includes Bullectomy, lung volume reduction surgery and lung transplantation.

Among the various agents currently available for the treatment of COPD and asthma, the focus of treatment is particularly recommended on bronchodilators. Within this class, inhaled therapy is generally preferred over systemic therapy due to improved efficacy and favorable margin of safety for additive benefits such as reduced side effects. Several options including short and long acting inhaled β_2-agonists, short and long acting inhaled anticholinergics, and methylxanthines exist for the treatment of COPD. Short acting bronchodilators may be used for patients with mild disease but long acting bronchodilators are more appropriate for patients with moderate to severe disease. In general, β_2-agonists act as a broad class of sympathomimetic agents, which include agents that stimulate α, β_1, and β_2 receptors [35,36]. Currently available β_2 selective therapies are classified depending upon the duration of action. These include albuterol, levalbuterol, pirbuterol, and terbutaline which act as short acting agents and formoterol, salmeterol and arformoterol as long acting agents whose action lasts for about 12 h [35].

Pharmacological treatment: Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and exercise tolerance. Commonly available agents used for the treatment of COPD include:

Bronchodilators: Bronchodilator medications are central to the symptomatic management of COPD. They are given either as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms [6]. Bronchodilator drugs commonly used in treating COPD include β_2-agonists, anticholinergics, and methylxanthines [7]. Short–acting bronchodilators can increase exercise tolerance acutely [51,52]. Long-acting inhaled β_2-agonists improve health status possibly due to a greater extent than regular short-acting anticholinergics, reduce symptoms, and rescue medication use and increase time between exacerbations compared with placebo [53-56]. Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Continuous use of a long-acting β_2-agonist or a short or long acting anticholinergic improves health status [53,57,58]. Treatment with a long acting inhaled anticholinergic drug reduces the rate of COPD exacerbations and improves the effectiveness of pulmonary rehabilitation [59,60]. Theophylline is a weak bronchodilator which may have some anti-inflammatory properties [61]. It is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available [7]. Combining short-acting bronchodilator agents (salbutamol (albuterol)/ipratropium) produces a greater change in spirometery than either agent alone [55]. Combining long-acting β_2-agonists and ipratropium leads to fewer exacerbations than either drug alone [56]. Tiotropium improves health status and reduces exacerbations and hospitalizations compared with both placebo and regular ipratropium [62,63].

Glucocorticoids: Glucocorticosteroids act at multiple points within the inflammatory cascade, although their effects in COPD are more modest as compared with bronchial asthma [60]. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic patients with COPD with an FEV_1 < 50% predicted (stages III and IV) and repeated exacerbations (e.g., three in the last 3 yr) [64-67]. This treatment has been shown to reduce the frequency of exacerbations and thus improve health status and withdrawal from treatment with inhaled glucocorticosteroids can lead to

exacerbations in some patients [68,69]. Many existing COPD guidelines recommend the use of a short course (2 weeks) of oral glucocorticosteroids to identify patients with COPD who might benefit from long-term treatment with oral or inhaled glucocorticosteroids [6]. Long-term treatment with oral glucocorticosteroids is not recommended in COPD [70,71]. Moreover, a side effect of long term benefit with systemic glucocorticosteroids is steroid myopathy which contributes to muscle weakness, decreased functionality and respiratory failure in patients with advanced COPD [6,71]. Some commonly used glucocorticosteroids are beclomethasone, budesonide, fluticasone, triamcinolone, prednisone and methylprednisone.

Other pharmacological treatments: Influenza vaccines can reduce serious illness and death in patients with COPD by approximately 50% [72]. Vaccines containing killed or live, inactivated viruses are recommended because they are more effective in elderly patients with COPD [73,74]. Regular use of mucolytics in COPD has been evaluated in a number of long-term studies [75-77]. Various mucolytic agents like ambroxol, erdosteine, carbocysteine, iodinated glycerol are commonly available. However, few patients with viscous sputum may benefit from mucolytics [78]. Oral and parenteral opioids are effective for treating dyspnea in patients with advanced COPD disease [79]. Various existing medications for COPD are out of scope of this article and are described elsewhere in detail.

Non pharmacological treatments: Pulmonary Rehabilitation: Pulmonary rehabilitation results in improvement in multiple outcome areas of considerable importance to the patient, including dyspnea, exercise ability, health status and healthcare utilization [80-84]. It is a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy [85]. The principle goals of this rehabilitation program are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of nonpulmonary problems, including exercise deconditioning, relative social isolation, altered mood states, muscle wasting, and weight loss. Patients with COPD at any stages of disease benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue [86]. Comprehensive pulmonary rehabilitation program also includes exercise training, nutrition counseling, and education [6].

Oxygen therapy: Oxygen therapy has a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics and mental state [87]. The primary goal of oxygen therapy is to increase the baseline partial pressure of oxygen in arterial blood (Pao_2) to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce a saturation of oxygen in arterial blood (Sao_2) of at least 90 %, which will preserve vital organ function by ensuring adequate delivery of oxygen [6,7]. Oxygen sources include gas, liquid and concentrator; while oxygen delivery methods include nasal continuous flow, pulse demand, reservoir cannulae and transtracheal catheters [88]. Overall, the key role of oxygen therapy is to preserve vital organ function by ensuring adequate delivery of oxygen.

Smoking cessation: Smoking cessation is the single most important and effective method of intervention to reduce the risk of the occurrence of COPD [37]. Quitting smoking can slow the progressive loss of lung function and can reduce symptoms at any point of time [89,90].

Mechanical ventilation: Noninvasive positive pressure ventilation should be offered to patients with exacerbation when, after optimal medical therapy and oxygenation, respiratory acidosis or excessive breathlessness persist [35, 37].

Breathing exercise: Breathing and physical exercises, as accessories to medical and surgical treatment were determined by Machmohan in 1915. Lip breathing results in a positive expiratory pressure and is thought to have similarities with continuous positive airway pressure and positive end expiratory pressure [91].

Surgical treatments: Bullectomy: This procedure is effective in reducing dyspnea and improving lung function [92]. A thoracic CT scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding suitability for resection of a bulla [7].

Lung Volume Reduction Surgery: This is a palliative surgical procedure. Patients with upper lobe emphysema and low exercise capacity who received the surgery had a greater survival rate than similar patients who received medical therapy [93,94]. In addition, the surgery patients experienced greater improvements in their maximal work capacity and their health related quality of life [7].

Lung Transplantation: In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity [95,96]. Single lung transplantation may be used for older patients with emphysema and patient with intrapulmonary restrictive disorders such as lung fibrosis. More recently, living lobar transplantation has been introduced [36].

Associated disorders: COPD is characterized by a range of pathological changes of the respiratory system including airflow limitation secondary to structural changes of the small airways, loss of alveolar attachments, inflammation, ciliary dysfunction and increased mucus production. It is evident that systemic manifestations are common in COPD. This disease also causes anaemia, sleep problem, anxiety, depression and several mental disorders. There are also many extrapulmonary effects such as systemic inflammation, nutritional abnormalities, weight loss, skeletal muscle dysfunction and additional organ effects [97,98].

Economic burden: Because of high prevalence of this disease and the potential for severe disability, COPD represents a substantial economic and social burden [99]. There are direct cost of healthcare services (admissions, medications, durable medical equipments) and indirect cost (lost work and productivity, premature death) that

can be included in total cost. One look at either attributable cost (cost related specifically to COPD) or excess costs (additional cost of treatment in COPD vs. non COPD patient for both COPD and non COPD illness) [100]. When adjusted to 1993 US dollars, the costs per capita are: $ 65 for the UK, $ 60 for Sweden and $ 87 for the USA [37]. Estimated direct cost of COPD in the US in 2004 was $ 20.9 billion. When the indirect cost of COPD due to lost productivity is included ($ 16.3 billion), the total societal cost of COPD is an estimated $ 37.2 billion. These numbers represent a significant economic burden on health care system worldwide [101].

Future perspectives: Focus of further research must be advanced so as to enhance our understanding of the molecular basis of COPD and to determine how this relates to the gross pathophysiological defects seen in these patients. Further, it requires identification and intervention in the basic disease process. COPD exerts a substantial burden on health care system globally and will continue to do so for the forceable future. Efforts should be made for future clinical trials and economic studies to harmonize study design and methods particularly toward adopting a universal modeling framework. Furthermore, the prospect for this disease in medical sciences alongwith improved innovations as well as patient care appears bright and quite emerging.

CONCLUSION

COPD is a systemic disease with debilitating and serious impact worldwide. It has been observed that prognosis of COPD in the developing countries is rather worse when compared to the developed world. Resolving the complex systemic nature as well as molecular basis of this ailment may allow the optimization of current therapeutic approaches alongwith novel intervention strategies leading to improvements in health status. Commendable research endeavors have been carried out for effective management of COPD. However, it must be emphasized that tobacco cessation strategies are crucial to prevent as well as arrest in the development of COPD. Finally, in heading towards the future, one cannot ignore the changing demographics of the world's population and the reality that COPD is a disease of ageing.

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