**Centenary Review Article**

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# Chronic obstructive pulmonary disease

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**The global prevalence of physiologically defined chronic obstructive pulmonary disease (COPD) in adults aged >40 yr is approximately 9-10 per cent. Recently, the Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults had shown that the overall prevalence of chronic bronchitis in adults >35 yr is 3.49 per cent. The development of COPD is multifactorial and the risk factors of COPD include genetic and environmental factors. Pathological changes in COPD are observed in central airways, small airways and alveolar space. The proposed pathogenesis of COPD includes proteinase-antiproteinase hypothesis, immunological mechanisms, oxidant-antioxidant balance, systemic inflammation, apoptosis and ineffective repair. Airflow limitation in COPD is defined as a postbronchodilator FEV1 (forced expiratory volume in 1 sec) to FVC (forced vital capacity) ratio <0.70. COPD is characterized by an accelerated decline in FEV1. Co morbidities associated with COPD are cardiovascular disorders (coronary artery disease and chronic heart failure), hypertension, metabolic diseases (diabetes mellitus, metabolic syndrome and obesity), bone disease (osteoporosis and osteopenia), stroke, lung cancer, cachexia, skeletal muscle weakness, anaemia, depression and cognitive decline. The assessment of COPD is required to determine the severity of the disease, its impact on the health status and the risk of future events (*e.g.*, exacerbations, hospital admissions or death) and this is essential to guide therapy. COPD is treated with inhaled bronchodilators, inhaled corticosteroids, oral theophylline and oral phosphodiesterase-4 inhibitor. Non pharmacological treatment of COPD includes smoking cessation, pulmonary rehabilitation and nutritional support. Lung volume reduction surgery and lung transplantation are advised in selected severe patients. Global strategy for the diagnosis, management and prevention of Chronic Obstructive Pulmonary Disease guidelines recommend influenza and pneumococcal vaccinations.**

**Key words** Airflow limitation - air pollution - bronchodilators - chronic obstructive pulmonary disease - exacerbations - lung - pulmonary rehabilitation - smoking

## Introduction

Chronic obstructive pulmonary disease (COPD) is a name coined for the diseases that were previously known as chronic bronchitis and emphysema. The British Medical Research Council (BMRC) defined chronic bronchitis as "daily productive cough for at least three consecutive months for more than two

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successive years[1]. American Thoracic Society (ATS) in 1962 defined emphysema as an "anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls"[2]. The definition of emphysema put forth by the National Heart, Lung and Blood Institute in 1984 is as "a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis"[3]. Reid reported that "the diagnosis of emphysema by itself is incomplete unless it is taken into account the presence or absence of chronic bronchitis and vice versa"[4]. McDonough *et al*[5] have recently reported extensive obliteration of terminal bronchioles in patients with COPD who have emphysema, suggesting that "the permanent enlargement of the distal airspaces may serve only as a structural biomarker, being a secondary result of small airway inflammation and destruction"[6]. Thus, COPD has both airway (central and small airways) and airspace abnormalities. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently defined COPD as "a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patient[7]". It is worthwhile to mention that William Osler in 1892 in his "Textbook of Medicine" has described hypertrophic emphysema as "a well-marked clinical affection, characterized by enlargement of the lungs due to distension of the air cells and atrophy of their walls, and clinically by imperfect aeration of the blood and more or less dyspnea"[8], a beautiful clinical description of emphysema.

## Epidemiology

### *(i) Global scenario*

There are wide variations in the prevalence of COPD across countries. This variation in the estimated prevalence is due to the method of diagnosis and classification of COPD[9]. It has been observed that the prevalence estimates were higher when COPD has been diagnosed by spirometry compared with methods using symptoms[10]. COPD is common in older population and is highly prevalent in those aged more than 75 yr. The global prevalence of physiologically defined chronic obstructive pulmonary disease (GOLD stage 2 or more) in adults aged ≥40 yr is approximately 9-10 per cent[11]. The Burden of Obstructive Lung Disease (BOLD) study from 12 sites involving 9425 subjects who had completed post bronchodilator spirometry testing found that the overall prevalence of COPD of GOLD stage II or higher was 10.1 per cent and the prevalence was 11.8 per cent for men and 8.5 per cent for women[12]. This study had also revealed that there were differences between countries, the prevalence ranging from 9 per cent in Reykjavik, Iceland to 22 per cent in Cape Town, South Africa for men and from 4 per cent in Hannover, Germany to 17 per cent in Cape Town for women.The multicentre PLATINO study that described the burden of COPD in five Latin American countries using post-bronchodilator spirometry had reported that the prevalence of airway obstruction was 14.3 per cent and the proportion of subjects in stages II-IV of the GOLD classification was 5.6 per cent[13]. The reported prevalence of COPD in China varied between 5 and 13 per cent in different provinces/cities[14].

### *(ii) Indian scenario*

One of the earliest studies to know the prevalence of COPD in India was carried out by Wig *et al* in 1964[15] in rural Delhi. The prevalence was 3.36 per cent in males and 2.54 per cent in females in this study. Viswanathan in 1966[16] reported 2.12 per cent prevalence in males and 1.33 per cent in females in Patna. Radha and colleagues[18] noticed that the prevalence in New Delhi in 1977 was 8.1 per cent in men and 4.6 per cent in women[17]. Jindal in 1993[18] reported that the prevalence was 6.2 per cent in men and 3.9 per cent in women in rural area, and 4.2 and 1.6 per cent, respectively in urban area. All these studies were from north India and information from south India was scanty. Thiruvengadam *et al* in 1977[19] from Madras (south India) reported the prevalence of COPD of 1.9 per cent in males and 1.2 per cent in females. However, Ray *et al* in 1995[20] from south India found that the prevalence was 4.08 per cent in males and 2.55 per cent in females. Recently, the Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARECH) involving a total of 85105 men, 84470 women from 12 urban and 11 rural sites was reported[21]. This study had shown that the overall prevalence of chronic bronchitis in adults >35 yr was 3.49 per cent (ranging 1.1% in Mumbai to 10% in Thiruvananthapuram). Thus there are wide variations in the prevalence of COPD in India subcontinent. Based on this study, the national burden of chronic bronchitis was estimated as 14.84 million.

## Risk factors

The development of COPD is multifactorial and the risk factors of COPD include genetic and environmental factors. The interplay of these factors is important in the development of COPD.

### *(i) Genetic factors*

Alpha1-antitrypsin deficiency is an established genetic cause of COPD especially in the young and it has been reported that α1-antitrypsin deficiency occurs in 1-2 per cent of individuals with COPD[22]. Alpha1- antitrypsin is mainly produced in the liver and normal alpha1 antitrypsin is due to the M allele. Severe alpha1-antitrypsin deficiency results from mutation in the SERPINA 1 gene [located on the long arm of chromosome 14 (14q31-32.3)] and this gives rise to the Z allele[23].

Genome-wide association (GWA) study has identified three loci (CHRNA3/CHRNA5/IREB2, HHIP, and FAM13A) that are associated with COPD susceptibility[24-26]. A new COPD locus has also been identified on chromosome 19q13, which harboured the *RAB4B*, *EGLN2*, *MIA*, and *CYP2A6* genes[27]. GWA study on forced expiratory volume in 1 second ($FEV_1$) and $FEV_1$/FVC (forced vital capacity) ratio has identified five genome-wide significant loci for pulmonary function, three [2q35 (*TNS1*), 4q24 (*GSTCD*), and 5q33 (*HTR4*)] for $FEV_1$, and two for FEV1/FVC [6p21 (*AGER*) and 15q23 (*THSD4*)][28]. Another GWA study found significant associations with $FEV_1$/FVC ratio for SNPs located in seven previously unrecognized loci: 6q24 (*GPR126*), 5q33 (*ADAM19*), 6p21 (*AGER* and *PPT2*), 4q22 (*FAM13A*), 9q22 (*PTCH1*), 2q36 (*PID1*), and 5q33 (*HTR4*). One new locus for FEV1 on 4q24 annotated by three genes (*INTS12*, *GSTCD*, and *NPNT*) was identified for FEV1[28]. 4q24 (*GSTCD*), 5q33 (*HTR4*) and 6p21 (*AGER*) were common in both studies[28,29]. The first GWA study on lung-function decline has recently reported one locus on chromosome 13q14.3 containing the *DLEU7* gene that is strongly associated with $FEV_1$ decline[30].

### *(ii) Environmental factors*

Tobacco smoking is the main cause of obstructive pulmonary disease[31]. Other important environmental factors associated with COPD are outdoor air pollution, occupational exposure to dusts and fumes, biomass smoke inhalation, exposure to second-hand smoke and previous tuberculosis[32].

*(a) Tobacco smoking*: Though tobacco smoking is the most important cause of COPD, the population-attributable fraction for smoking as a cause of COPD ranged from 9.7 to 97.9 per cent[32]. A Swedish cohort study had observed that population-attributable fraction for smoking as a cause of COPD was 76.2 per cent[33]. In another Denmark study, the reported population-attributable fraction as a cause of COPD was 74.6 per cent[34]. Thus, a significant proportional subjects with COPD had causes other than tobacco smoking. In our country, *bidi* smoking is an important factor in addition to cigarette smoking that causes COPD[35].

*(b) Outdoor air pollution*: Outdoor air pollution mainly from emission of pollutants from motor vehicles and industries is an important public health problem[36]. In a community-based study, it has been observed that higher traffic density was significantly associated with lower FEV1 and FVC in women[37]. In the Danish Diet, Cancer and Health cohort study involving 57,053 participants, it has been shown that COPD incidence was significantly associated with nitrogen dioxide levels[38]. Particulate pollutants, ozone and nitrogen dioxide can produce bronchial hyper reactivity, airway oxidative stress, pulmonary and systemic inflammation[36]. However, a causal relationship between outdoor air pollution and COPD is still not established.

*(c) Indoor air pollution:* Important indoor air pollutants are environmental tobacco smoke, particulate matter, nitrogen dioxide, carbon monoxide, volatile organic compounds and biological allergens[37]. Among these, environmental tobacco smoke[39,40] and biomass smoke exposure are related to the development of COPD[42]. Globally, it has been estimated that about 2.4 billion people (about 50% of world's population) use biomass fuel as the primary energy source for domestic cooking, heating and lighting[43]. Biomass (wood, crop residue and animal drug) are burnt in rural areas using substandard stoves in poorly ventilated indoors. Women, spending more time indoors for cooking than men, are exposed to biomass fuel combustion products and are prone to develop COPD[41,42,44]. A meta-analysis has shown that biomass smoke exposure was a risk factor for developing COPD in both women and men[44].

*(d) Other risk factors*: Other risk factors associated with COPD and reduced FEV1 are occupational exposure to dusts and fumes, previous tuberculosis, maternal smoking, childhood asthma and childhood respiratory infections[45].

## Pathology

Pathological changes in COPD are observed in central airways, small airways and alveolar space[46].

Mucus glands and goblet cells are found in the lining of trachea-bronchial tree in normal individuals and mucus is produced by these cells. In chronic bronchitis patients, the mucus glands are enlarged and goblet cells undergo metaplasia. The excess mucus secreted by these cells as a result of irritation from cigarette smoke, air pollutants, *etc.* and cough are the cardinal features of chronic bronchitis. The size of the mucus glands can be determined by the Reid index which is measured by calculating the ratio of bronchial gland to the thickness of bronchial wall[4]. Narrowing and destruction of terminal bronchioles (airways <2 mm in diameter) are characteristic changes in COPD. Small airways offer <20 per cent of the total resistance below the larynx[47] and the resistance of the small airways is increased 4- to 40-fold in lungs from patients with COPD[48]. Thus, the small airways are the major site of increased resistance in persons with COPD. The cellular events that occur in the small airways in COPD include replacement of Clara cells with mucus-secreting and infiltrating mononuclear cells and goblet cell metaplasia[46]. Smooth muscle hypertrophy is also an important finding. As a result of excess mucus secretion, oedema formation and cellular infiltration and the resultant fibrosis cause airway narrowing. Pathological changes that occur in alveolar space include accumulation of macrophages and neutrophils. There is also an increase in T-lymphocytes particularly $CD8^+$ T cells. Chronic inflammation and destruction of alveolar space lead to either cetriacinar or panacinar emphysema.

**Pathogenesis**

The proposed pathogenesis of COPD includes proteinase-antiproteinase hypothesis, immunological mechanisms, oxidant-antioxidant balance,systemic inflammation, apoptosis and ineffective repair[46].

***(i) The proteinase-antiproteinase hypothesis***

The proteinase-antiproteinase hypothesis is based on the assumption that tissue destruction and emphysema occur due to an imbalance between the proteinases and their inhibitors. It has been proposed that there is an increase in the quantity of elastic-degrading enzymes compared to their inhibitors in emphysema. This concept has been suggested in emphysema that has been described in $\alpha_1$ antitrypsin ($\alpha_1$AT) deficiency, first reported by Laurell and Eriksson in 1963[49]. The patients with $\alpha_1$AT deficiency have mutations in the *$\alpha_1$AT* gene. Z mutation is the common mutation and these mutations impair secretion of the protein from hepatocytes. As a result, there is markedly decreased circulating level of serine proteinase inhibitor. PiZ-$\alpha_1$AT is less effective than the normal PiM-$\alpha_1$AT. It has been recently reported that PiZ-$\alpha_1$AT is prone to polymerization which can inhibit hepatic secretion, impair neutrophil elastase (NE) inhibition and promote inflammation[46]. Chronic cigarette smoke exposure leads to accumulation of activated macrophages, neutrophils and $CD8^+$ T lymphocytes in the distal airways and alveolar spaces[50]. Macrophages and neutrophils are the main sources of proteases in lungs. Excess neutrophil elastase produced by the activated neutrophils overwhelms the serine proteinase inhibitors leading to the development of emphysema. Cigarette smoke also activates airway epithelium to trigger airway remodelling[51]. Studies have demonstrated that there are correlations between the degree of macrophage and neutrophil inflammation and severity of airflow obstruction[52].

Matrix metalloproteinases (MMP), increased in many lung diseases including COPD, have the capacity to cleave structural proteins such as collagen and elastin and these MMPs are linked to the pathogenesis of COPD[53]. Increases in many MMPs are reported in smoking-related emphysema and three MMPs (MMP-2, -9, and 12) are shown to degrade elastin[53]. MMP-9 and MMP-12 are expressed in alveolar macrophages from COPD patients. Cigarette smoke causes macrophages to produce MMP-12 which can cleave elastin into fragments. Elastin fragments are chemotactic to monocytes and fibroblasts and this increases the inflammatory and protease burden in the lung and leads to subsequent lung destruction. This creates a positive feedback loop that results in continuous destruction of lung parenchyma[54]. A single-nucleotide polymorphism in MMP-12 has been identified as a protective factor for COPD[55]. Other proteases that play important roles in COPD are cathapsins S, L (in macrophages), and G, and proteinase-3 (in neutrophils)[56]. However, subsequent studies have unravelled a more complex pathogenesis in emphysema[57].

***(ii) Immunological mechanisms***

COPD is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, most commonly cigarette smoke[7]. Patients with COPD have been reported to have increased numbers of neutrophils in sputum, lung tissue and bronchoalveolar lavage (BAL)[58] and neutrophils are important cells in the pathogenesis of COPD. Serum levels of

immunoglobulin free light chains (IgLC) were found to be increased in smoking-induced COPD[59]. IgLC were found to bind neutrophils and cross-linking of IgLC on neutrophils results in increased production of IL8/CXCL8 which is a selective attractant of neutrophils. B cells have been found to be increased in COPD and these cells produce IgCL, in addition to IgG and IgA in COPD[60]. It has also been reported that serum IgE levels are increased in patients with COPD and this may be related to smoking[61]. Both IgE and IgLC can exert similar proinflammatory effects via neutrophils[59]. However, the role of immunoglobulins in the pathogenesis of COPD is not understood.

***(iii) Oxidant-antioxidant balance***

Abnormally accumulated inflammatory cells including neutrophils and macrophages and cigarette smoke produce reactive oxygen species which play an important role in the pathogenesis of COPD. Oxidative stress can impair vasodilation and endothelial cell growth. When the oxidant load exceeds the antioxidant capacity of the lung, modification of proteins, lipids, carbohydrates and DNA occurs in the local milieu resulting in tissue injury. Though the oxidants cannot degrade extracellular matrix, these can modify elastin. Modified elastin is then more susceptible to proteolytic cleavage. Cigarette smoke can inactivate histone deacetylase (HDAC2) and this leads to NF-kB-mediated transcription of neutrophil chemokines/cytokines (TNF-α and IL-8) and MMPs. Neutrophil elastase and MMPs overwhelm their respective inhibitors. This can augment the matrix-degrading capacity which can promote emphysema formation[46].

***(iv) Systemic inflammation***

In addition to the pulmonary component, COPD has several extrapulmonary manifestations. It has been postulated that persistent pulmonary inflammation may promote the release of pro-inflammatory chemokines and cytokines into the circulation[62]. These mediators can stimulate liver, adipose tissue and bone marrow to release excessive amounts of leucocytes, C-reactive protein (CRP), interleukin (IL)-6, IL-8, fibrinogen and tumour necrosis factor-α (TNF-α) into the circulation[62,63]. This may lead to a persistent low-grade systemic inflammation[62]. Systemic inflammation may initiate or worsen comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes[64]. Two Danish population studies involving 8656 COPD patients had revealed that simultaneously elevated levels of CRP, fibrinogen, and leukocyte count were associated with a 2- to 4-fold increased risk of major comorbidities (myocardial infarction, heart failure, diabetes, lung cancer and pneumonia) in COPD[65].

***(v) Apoptosis***

Recent studies have highlighted that apoptosis is involved in the development of COPD and it has been demonstrated that there is an increase in apoptotic alveolar epithelial and endothelial cells in the lungs of COPD patients. Since this is not counterbalanced by an increase in proliferation of these structural cells, the net result is destruction of lung tissue and the development of emphysema. It has been suggested that there is a role for vascular endothelial growth factor (VEGF) in the induction of apoptosis of structural cells in the lung. Other mediators involved in apoptosis are caspase-3 and ceramide[51,66-68].

***(vi) Ineffective repair***

There is ineffective repair in emphysema and this is due to the limited ability of the adult lung to repair the damaged alveoli. Studies have shown that treatment of normal rats with all-trans-retinoic acid increases the number of alveoli and this prompted the investigators to study whether a similar effect would occur in rats with emphysema. In experimentally produced emphysema in rats, it has been shown that treatment with all-trans-retinoic acid reversed the changes associated with emphysema. A similar effect in humans is a possibility[69]. Advances in regenerative medicine and stem cell biology may answer some of these issues.

***(vii) Endothelial microparticles***

Pulmonary vascular disease is an important consequence of COPD. Endothelial microparticles (EMPs) which are microvesicles released from apoptotic endothelial cells are increased in smokers with normal spirometry and low diffusing capacity[70]. The majority of microparticles are angiotensin-converting enzyme positive and this observation suggests that EMPs are of pulmonary vascular origin. EMPs can be a potential biomarker for pulmonary vascular disease associated with COPD.

**Pathophysiology**

Pathophysiological changes in COPD are due to the pathological changes seen in central airways, small peripheral airways, pulmonary parenchyma and pulmonary vasculature. Mucus hypersecretion

is common in patients with predominant central airway involvement. Chronic obstructive pulmonary disease is characterized by an accelerated decline in FEV1[71]. Airflow limitation in COPD is defined as a postbronchodilator FEV1 (forced expiratory volume in 1 sec) to FVC (forced vital capacity) ratio <0.70, usually without reversibility to bronchodilators. Bronchodilator reversibility and bronchial hyper-reactivity are variable in COPD and, therefore, have limited value in distinguishing COPD from bronchial asthma[72]. Overall 23 to 42 per cent of patients with COPD have responsiveness to bronchodilators and 59 per cent of men and 85 per cent of women with moderate COPD have airway hyper responsiveness[73,74]. The severity of airflow limitation in COPD is classified based on post-bronchodilator FEV1value into four groups (GOLD 1, GOLD 2, GOLD 3 and GOLD 4). In patients with FEV1/FVC <70, if FEV1 >80 per cent predicted, they are classified as mild (GOLD 1), if FEV1 predicted < 80 per cent and ≥ 50 per cent as moderate (GOLD 2), if FEV1 predicted <50 per cent and >30 per cent as severe (GOLD 3) and if FEV1 predicted <30 per cent as very severe (GOLD 4) airflow limitation[7]. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study has shown that the rate of decline in FEV1 over a 3-year period was highly variable[76]. In this study, the mean rate of change in FEV1 was a decline of 33 ml per year with significant variation and only 38 per cent of patients had an estimated decline in FEV1 of more than 40 ml per year. The rate of decline in FEV1 in this study in more than half of the patients was no greater than that observed in subjects without lung disease suggesting that COPD is not invariably progressive. Current smokers, patients with bronchodilator reversibility, and patients with emphysema had increased rates of decline in FEV1[75]. The ECLIPSE study further observed that Clara cell protein (CC-16) was significantly associated with a greater decline in FEV1 of 4 ± 2 ml per year for each decrease in one standard deviation of the CC-16 level[75]. Patients with COPD have pulmonary hyperinflation characterized by an increase in functional residual capacity and a decreased inspiratory capacity. Patients with emphysema have low carbon monoxide diffusing capacity. Low arterial oxygen and high carbon dioxide levels are observed in patients with COPD with respiratory failure. Pulmonary arterial hypertension (PAH) develops late in the course of the natural history of patients with COPD. This can be associated with the development of severe hypoxaemia and is a major cardiovascular complication of COPD. Chronic pulmonary hypertension leads to the development of right ventricular hypertrophy and cor pulmonale and has a poor prognosis[76]. Wells *et al*[77] observed that computerised tomography-detected pulmonary artery enlargement defined as a ratio of the diameter of the pulmonary artery to the diameter of the aorta (PA: A ratio of >1) was independently associated with acute exacerbations of COPD[77].

**Co-morbidities**

Extrapulmonary manifestations in COPD, in addition to pulmonary component, are common. It has been observed in the ECLIPSE study that comorbidities were significantly higher in patients with COPD than in smokers and never smokers[78]. The important comorbidities associated with COPD are cardiovascular disorders (coronary artery disease and chronic heart failure, hypertension), metabolic diseases (diabetes mellitus, metabolic syndrome and obesity), bone disease (osteoporosis and osteopenia), stroke, lung cancer, cachexia, skeletal muscle weakness, anaemia, depression and cognitive decline[79]. Risk factors such as advancing age, cigarette smoking and environmental pollution are common to both COPD and ischaemic heart disease. The potential mechanisms of increased risk of cardiovascular disease in COPD are systemic inflammation, increased oxidative stress, neurohumoral disturbances and increased thrombotic tendency[62]. A systematic review of literature had shown that reduced FEV1 nearly doubles the risk for cardiovascular mortality independent of age, sex and cigarette smoking[80]. It has been reported that a 10 per cent decrease in FEV1 among COPD patients increases the cardiovascular event rate 28 per cent[81]. COPD patients were 1.76 times more likely to have arrhythmias, 1.61 times more likely to have angina, 1.61 times more likely to develop acute myocardial infarction and 3.84 times more likely to develop congestive heart failure[82]. There was also an inverse relationship between lung function and ischaemic stroke in subjects who had never smoked[83]. In a study of 12,04,110 patients aged >35 yr, COPD patients (n=29870) were five times more likely to have a cardiovascular disease compared with those without COPD (n=11,74,240)[84]. Analysis of data from 20,296 subjects aged ≥45 yr at baseline in the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS) has revealed that subjects with GOLD stages 3 or 4 COPD had a higher prevalence of diabetes, hypertension and cardiovascular disease[85]. Lucas-Ramos *et al*[86] in a study of 1200 COPD patients and 300 control subjects showed that the COPD group had a significantly higher

prevalence of ischaemic heart disease, cerebrovascular disease, and peripheral vascular disease. COPD, hypertension, diabetes, obesity, and dyslipidaemia were risk factors for ischaemic heart disease in the univariate analysis. In the multivariate analysis adjusted for the remaining factors, COPD was still an independent risk factor suggesting that COPD patients had a high prevalence of cardiovascular disease, higher than expected given their age and the co-existence of classic cardiovascular risk factors[86].

Cachexia, defined as excessive weight loss is a frequent finding in COPD and is associated with poor functional capacity and increased mortality. It has been observed that 10 to 15 per cent of patients with mild to moderate COPD have significant weight loss whereas the weight loss is observed in 50 per cent of patients with severe COPD[87]. It has been reported that fat-free mass is significantly reduced in COPD[61]. The proposed mechanism of cachexia in COPD includes low testosterone levels, increased pro-inflammatory cytokines and increased catecholamine synthesis[88-90].

Skeletal muscle dysfunction due to loss of skeletal muscle mass occurs mainly in the thighs and upper arms[91]. As a result of skeletal muscle dysfunction, patients with COPD have reduced exercise endurance and present with symptoms of fatigue and dyspnoea[92]. There was significant reduction in type I fibres and a relative increase in type II fibres in skeletal muscles of patients with COPD[93]. Reduced oxidative energy metabolism as a result of the reduced cytochrome C oxidase and succinate dehydrogenase activities has been reported in COPD[94]. Microscopic findings in skeletal muscles of COPD patients include increased oxidative stress, lactic acidosis, increased apoptosis and inflammatory changes[95]. Deconditioning and disuse are other factors that may contribute to skeletal muscle dysfunction. Use of corticosteroids, poor nutrition and hormonal changes exaggerate muscle dysfunction in COPD[96].

Another important comorbid condition in COPD is reduced bone mass. A strong correlation between low bone mass and radiological emphysema has been reported in smokers[97]. The risk of osteoporosis increases by 1.9-fold in patients with airway obstruction compared with those without airway obstruction and by 2.4-fold in patients with severe COPD[98]. The proposed aetiology for the bone loss includes smoking, vitamin D deficiency, low body mass index, hypogonadism, sedentary lifestyle, and use of glucocorticoids[99]. Patients with COPD are vulnerable to fractures particularly vertebral fractures[100].

Epidemiological studies have suggested that the risk of lung cancer is higher in smokers with COPD compared with smokers with normal lung function[101,102]. Previous lung diseases are also found to be associated with an increased risk of lung cancer[101]. The annual-incidence rates of lung cancer per 10,000 person-years were at least four-fold higher in patients with prior COPD compared with the general population [102]. A longitudinal study has revealed that there is high incidence density of lung cancer in outpatients with COPD (16 per 1000 person- years compared with 1-1.5 per persons in smokers with normal lung function)[103]. This study has also shown that the most frequent type of lung cancer was squamous cell carcinoma (44%) and lung cancer incidence was lower in patients with worse severity of airflow obstruction. GOLD stages I and II, older age, lower body mass index, and lung diffusion capacity of carbon monoxide less than 80 per cent were associated with lung cancer diagnosis[103].

Depressive symptoms were found to be common among patients with COPD[104]. In a study consisting of 2,118 subjects with COPD, 335 smokers without COPD (smokers), and 243 non-smokers without COPD (non-smokers), 26, 12, and 7 per cent of COPD, smokers, and non-smokers, respectively have been found to suffer from depression. In subjects with COPD, higher depression prevalence was seen in females, current smokers, and those with GOLD-defined severe disease[105]. Frontal-type cognitive decline with the worsening of the hypoxemia has been reported in COPD[106].

Anaemia was observed in 17 per cent of patients with COPD compared to 6 per cent seen with polycythemia and anaemia was an independent risk factor for reduced functional capacity in COPD[107].

**Exacerbations**

Exacerbation in COPD is defined as an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication[7]. COPD exacerbations are important because they are associated with significant morbidity, health care cost and mortality[108]. Several factors exacerbate COPD and the common factors are bacterial or viral respiratory tract infections. Air pollution is another contributing factor. The cause of exacerbations cannot

be identified in one-third of cases. Patients with 2 or more exacerbations per year are classified as "frequent exacerbators". A new patient-reported outcome diary known as EXAcerbation of Chronic Pulmonary Disease Tool (EXACT) has been developed to evaluate the frequency, severity, and duration of exacerbations of COPD and this 14-item daily diary has been found to be reliable, valid, and sensitive to changes during recovery from exacerbation[109]. Bafadhel *et al*[110] using unbiased analysis have identified four distinct biologic exacerbation clusters and these were bacterial, viral, eosinophilic and pauci inflammatory. They have also found that sputum IL-1β, serum CXCL10, and peripheral eosinophils are biomarkers of bacteria-, virus-, or eosinophil associated exacerbations of COPD[110]. Tanabe *et al*[111] reported that annual changes in CT parameters of emphysema are greater in patients with a history of exacerbations of COPD than in those without a history of exacerbations suggesting that exacerbations accelerate emphysema progression in patients with COPD[111]. A systematic review of the literature to determine the prevalence of pulmonary embolism in acute exacerbations of COPD had revealed that one of four COPD patients who require hospitalization for an acute exacerbation might have pulmonary embolism[112].

The diagnosis of exacerbation is based on the acute change of symptoms (baseline dyspnoea, cough and/or sputum production) that is beyond normal day-to-day variation. Differential diagnosis of COPD exacerbations includes pneumonia, pulmonary embolism, congestive cardiac failure, cardiac arrhythmias, pneumothorax and pleural effusion. These conditions may mimic and/or aggravate exacerbations and have to be treated if identified. The assessment of severity of exacerbations can be assessed by pulse oxymetry (for adjusting supplemental oxygen therapy), arterial blood gases (for diagnosis of acute-on-chronic respiratory failure), acid-base status (for initiating mechanical ventilation), chest X-rays to exclude alternate causes, electrocardiogram to diagnose cardiac conditions and whole blood count to identify polycythemia, anaemia or leucocytosis. In addition, the presence of purulent sputum is an indication for initiating empiric antibiotic treatment. Common pathogens in an exacerbation are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. *Pseudomonas aerugenosa* can be identified in COPD patients belonging to the GOLD groups 3 and 4. Electrolyte abnormalities and hyperglycaemia may be due to the associated co-morbidities[87].

## Management

### *(i) Pharmacological agents*

The drugs for treatment of COPD are inhaled bronchodilators, inhaled corticosteroids, oral theophylline and oral phosphodiesterase-4 inhibitor. Oxygen therapy is indicated in COPD patients with chronic respiratory failure with hypoxemia.

*(a) Bronchodilators:* Inhaled bronchodilators are the main pharmacological agents that improve symptoms, decrease exacerbations and improve quality of life in COPD[113]. Bronchodilators can cause only a small (<10%) increase in FEV1 in patients with COPD. Though there is only a small improvement in spirometric measurements, bronchodilators may improve symptoms especially dyspnoea by reducing hyperinflation[114,115]. Inhaled bronchodilators can be either $\beta_2$-adrenergic receptor agonists or cholinergic receptor antagonists. $\beta_2$-adrenergic receptor agonists can be short-acting (*e.g.* salbutamol) or long-acting (*e.g.* formoterol fumarate and salmeterol xinafoate). Similarly, cholinergic receptor antagonists can be short-acting (*e.g.* ipratropium bromide) or long-acting (*e.g.* tiotropium bromide). The duration of action of inhaled short-acting $\beta_2$-agonists is 4 to 6 h and that of short-acting inhaled anticholinergics lasts up to 8 h. The duration of action of inhaled long-acting $\beta_2$-agonists is 12 h or more and the action of inhaled long-acting anticholinergics lasts more than 24 h. The adverse effects of inhaled short-acting $\beta_2$-agonists include sinus tachycardia, somatic tremor and hypokalemia. The important adverse effects of inhaled anticholinergics are dry mouth and occasional prostatic symptoms.

Patients with mild airflow limitation can be treated with a single short-acting inhaled bronchodilator, either with salbutamol or with ipratropium. Both drugs are equally effective to relieve symptoms and to improve airflow. Patients with moderate airflow limitation require treatment with either a long-acting $\beta_2$-adrenergic receptor agonist (formoterol or salmeterol) or long-acting cholinergic receptor antagonist (tiotropium). A short-acting bronchodilator (not a long-acting inhaled bronchodilator) is the appropriate treatment for relief of acute symptoms. Combination of short-acting bronchodilators, a $\beta_2$-adrenergic receptor agonist and a cholinergic receptor antagonist (*e.g.* salbutamol and ipratropium) has been shown to have a greater bronchodilation than either drug used alone[116]. Combining a long-acting $\beta_2$-adrenergic receptor agonist (*e.g.* salmeterol) with a short-acting

cholinergic receptor antagonist (*e.g.* ipratropium) has been shown to improve airways obstruction[117]. In a randomized, double-blind trial in patients with COPD, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study has demonstrated that treatment with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV1[118]. In a 1-year, randomized, double-blind, double-dummy, parallel-group trial, the investigators of the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial reported that tiotropium (18 µg once daily) is more effective than salmeterol (50 µg twice daily) in preventing exacerbations in patients with moderate-to-very-severe COPD[119].

Glycopyrronium is a novel long-acting anticholinergic and is a synthetic quaternary ammonium compound acting as a competitive antagonist by binding to muscarinic receptors in bronchial smooth muscle. It is currently in development for the treatment of COPD. The effect of glycopyrronium (50 µg) is similar to that of tiotropium in reducing dyspnoea and the risk of exacerbations, as well as improving lung function, exercise tolerance, and health status in patients with COPD[120,121].

Indacaterol is an "ultra" long-acting $\beta_2$-adrenergic agonist that is distinguished by once-daily dosing. The duration of action of inhaled indacaterol is >24 h compared to twice-daily dosing of other long-acting $\beta_2$-adrenergic agonists such as salmeterol and formoterol that have a bronchodilator action of about 12 h. Indacaterol has a fast onset and produces sustained bronchodilation. It relaxes bronchial smooth muscles to reduce the symptoms of COPD and is well tolerated. Indacaterol is intended for the long-term maintenance treatment of COPD[122]. Indacaterol (150 or 300 µg) was found to be an effective once-daily bronchodilator and was at least as effective as tiotropium in improving clinical outcomes for patients with COPD[122]. Indacaterol 150 µg administered once daily had been shown to have a clinically relevant bronchodilator effect over 24 h post-dose and improved health status and dyspnoea to a greater extent than twice-daily 50 µg salmeterol[123]. Indacaterol given to COPD patients for one year was well tolerated and provided significant and well-maintained bronchodilation that was accompanied by improved clinical outcomes[124]. Feldman *et al*[125] had shown that low dose (75 µg) of indacaterol can be used for maintenance therapy for patients with COPD and indacaterol at this dose showed positive benefit in both decreasing dyspnoea and improving quality of life. The US FDA has approved 75 µg once-daily dose of indacaterol for use as a long-term maintenance treatment for patients with COPD[126].

*(b) Corticosteroids*: The fact that COPD is associated with chronic inflammation is the rational for the use of inhaled corticosteroids in COPD. There is no evidence that inhaled or oral steroids suppress inflammation in COPD[127]. This is in contrast to the beneficial effects of inhaled steroids in the treatment of chronic asthma. However, there are evidences that inhaled and systemic steroids have beneficial effects in acute exacerbations of COPD[128,129]. Inhaled steroids have been shown to improve symptoms, lung function, quality of life and to reduce the frequency of exacerbations in COPD patients with FEV1 <50 per cent predicted[130-132]. Adverse effects of inhaled corticosteroids are oral candidiasis, hoarseness of voice and skin bruising. Long-term treatment with inhaled corticosteroids has been shown to be associated with an increased risk of pneumonia[130,133,134]. Oral corticosteroids are not recommended as long-term monotherapy in COPD patients and have numerous side effects if administered long-term.

*(c) Phosphodiesterase inhibitors*: Theophylline, a weak oral bronchodilator is a non-selective phosphodiesterase inhibitor and has some anti-inflammatory properties. However, its narrow therapeutic index is a concern requiring frequent monitoring of blood levels, adverse drug reactions and drug interactions. COPD patients, if continued to be symptomatic despite combined inhaled bronchodilator treatment, can be prescribed theophylline and it provides additional improvement in lung function with a few exacerbations[135]. Important adverse effects of theophylline are atrial and ventricular arrhythmias, convulsions, headache, insomnia and nausea. Theophylline has also interactions with many commonly used medications.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor and it reduces inflammation by inhibiting the breaking down of intracellular cyclic AMP. It is administered orally with a once a day schedule (500 mg) and it reduces acute exacerbations in patients with COPD[136]. Roflumilast used concomitantly with long-acting $\beta_2$ agonists has been shown to reduce exacerbations in COPD[137,138]. Adverse reactions with roflumilast include nausea, diarrhoea, sleep disturbances, headache, and weight loss.

***(ii) Pharmacotherapy***

The clinical diagnosis of COPD is based on the history of progressive and persistent dyspnoea that worsens with exercise, chronic cough which may be initially intermittent and may be unproductive, chronic sputum production of any pattern, history of exposure to risk factors (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals) and a family history of COPD[7]. Spirometry is required to confirm the presence of persistent airflow limitation which is defined as the presence of post-bronchodilator FEV1/FVC <70.

*(a) Assessment of disease:* The assessment of COPD is required to determine the severity of the disease, its impact on the health status and the risk of future events (*e.g*. exacerbations, hospital admissions or death) and this is essential to guide therapy. Assessment of COPD is achieved by considering the patient's current symptoms, the severity of spirometric abnormality, the exacerbation risk and the presence of comorbidities separately. GOLD guidelines recommend Modified British Medical Council (mMRC) questionnaire or COPD Assessment Test (CAT) to assess symptoms[139,140]. Spirometric assessment is required to classify the severity of airflow limitation. Spirometric evaluation is to be done after administration of inhaled short-acting bronchodilator. The best predictor of having frequent exacerbations (2 or more exacerbations per year) is a history of previous treated events[141] and worsening airflow limitation is also associated with an increasing prevalence of exacerbations and risk of death[7]. Assessment of comorbidities is essential in COPD, as these can influence mortality and hospitalizations in COPD[85].

Combined COPD assessment is based on the combination of the symptomatic assessment with the spirometric classification and/or risk of exacerbations. The assessment of symptoms based on mMRC questionnaire or CAT scale indicates the level of symptoms. A high level of symptom is indicated when the mMRC grade is >2 or the CAT score is >10. Only one scale either mMRC grade or CAT scale is sufficient to assess the symptoms, preferring the CAT scale. Exacerbation risk can be assessed by using GOLD spirometric classification and by the individual patient's history of exacerbations. GOLD spirometric categories 3 or 4 and two or more exacerbations in the preceding year indicate high risk. If the risk assessment done based on spirometric categories or exacerbation history shows any discrepancy, the assessment that provides the highest risk is to be used. Combined COPD assessment done as mentioned provides four groups as follows[7]:

Group A (Low risk, less symptoms): GOLD 1 or 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade 0-1 or CAT score <10.

Group B (Low risk, more symptoms): GOLD 1 or 2 (mild or moderate airflow limitation) and/or 0-1 exacerbation per year and mMRC grade >2 or CAT score >10.

Group C (High risk, less symptoms): GOLD 3 or 4 (severe or very severe airflow limitation) and/or >2 exacerbation per year and mMRC grade 0-1 or CAT score <10.

Group D (High risk, more symptoms): GOLD 3 or 4 (severe or very severe airflow limitation) and/or >2 exacerbation per year and mMRC grade >2 or CAT score >10.

Group A patients are treated with a short-acting bronchodilator (either short-acting anticholinergic or short-acting $\beta_2$-agonist) as the first choice. The second choice is a combination of short-acting bronchodilators (short-acting anticholinergic and short-acting $\beta_2$-agonist) or a long-acting bronchodilator (either long-acting anticholinergic or long-acting $\beta_2$-agonist). Theophylline is an alternative choice.

Group B patients can be treated with a long-acting bronchodilator (either long-acting anticholinergic or long-acting $\beta_2$-agonist). Patients with severe breathlessness in group B can be treated with a combination of long-acting anticholinergic and long-acting $\beta_2$-agonist. Alternate choice is short-acting bronchodilators (short-acting anticholinergic and/or short-acting $\beta_2$-agonist) and theophylline.

Group C patients require treatment with a fixed combination of inhaled corticosteroids and long-acting $\beta_2$-agonist or long-acting anticholinergic. The second choice of treatment is with a combination of long-acting anticholinergic and long-acting $\beta_2$-agonist. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting $\beta_2$-agonist) and theophylline. A phosphodiesterase-4 inhibitor can also be added.

Group D patients can be treated with a fixed combination of inhaled corticosteroids and long-acting

$\beta_2$-agonist or long-acting anticholinergic. Different drug combinations are recommended as second choice for treatment of group D patients. The combinations are inhaled corticosteroid and long-acting anticholinergic or inhaled corticosteroid + long-acting $\beta_2$-agonist and long-acting anticholinergic or inhaled corticosteroid + long-acting $\beta_2$-agonist and phosphodiesterase-4 inhibitor or long-acting $\beta_2$-agonist and long-acting anticholinergic or long-acting anticholinergic and phosphodiesterase-4 inhibitor. Alternate treatment is with short-acting bronchodilators (short-acting anticholinergic and/or short-acting $\beta_2$-agonist) and theophylline and carbocysteine.

*(b) Oxygen therapy*: Patients with COPD with respiratory failure and with severe resting hypoxemia on long-term oxygen therapy (LTOT) (>15 h per day) have been found to have increased survival. LTOT is prescribed to COPD patients with $PaO_2$ <7.3 kPa (55 mm Hg) or $SaO_2$ <88 per cent with or without hypercapnia confirmed twice over a three week period or $PaO_2$ between 7.3 kPa (55 mm Hg) and 8 kPa (60 mm Hg) with evidence of pulmonary hypertension, peripheral oedema indicating congestive cardiac failure or polycythemia (haematocrit >55)[142,143].

*(c) Exacerbations*: The treatment of exacerbations in COPD is with bronchodilators, corticosteroids and antibiotics. Short-acting inhaled $\beta_2$-agonists or short-acting anticholinergics are the preferred bronchodilator for the treatment of exacerbations[144]. Short-acting bronchodilators can be given either by metered-dose inhalers or by nebulizers and there are no differences in FEV1 whether given by metered-dose inhalers or by nebulizers[145]. When there is insufficient response to inhaled short-acting bronchodilators, intravenous methylxanthines (theophylline or aminophylline) can be given, keeping in mind the adverse effects and drug interactions of methylxanthines[146,147]. Systemic corticosteroids have been found to shorten recovery time and arterial hypoxemia[129,148]. The systemic corticosteroids also reduce the risk of early relapse, treatment failure and length of hospital stay[148,149]. Oral prednisolone 30-40 mg daily is given for 10-14 days. Alternative treatment is with nebulized budesonide. Increase in dyspnoea, sputum volume and sputum purulence are the cardinal features of exacerbations in COPD. Antibiotics for 5 to 10 days are prescribed if two of the three cardinal symptoms (increased purulence of symptoms is one of the symptoms) are observed. The COPD Clinical Research Network undertook a study to determine whether azithromycin decreased the frequency of exacerbations in patients with COPD, as macrolide antibiotics have immunomodulatory, anti-inflammatory, and antibacterial effects[150]. COPD patients (n=1142) with a history of prior exacerbation were randomised to receive azithromycin 250 mg daily or a placebo and continued their usual care. The study showed that azithromycin 250 mg daily taken daily for 1 year , when added to usual treatment in COPD patients, decreased the frequency of exacerbations and improved quality of life. However, azithromycin caused hearing decrements in a small percentage of subjects[151]. Supplemental oxygen is required to maintain arterial oxygen saturation 88 to 92 per cent. Ventilatory support either non-invasive mechanical ventilation or mechanical ventilation based on proper indications is required in patients in COPD patients with severe exacerbations admitted to hospitals.

***(iii) Non-pharmacologic treatment***

*(a) Smoking cessation*: Smoking cessation is the most important step in the treatment of COPD. Smoking cessation has been found to reduce the decline of FEV1[152]. Nicotine replacement treatment with nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet or lozenges has been found to increase long term smoking-abstinence rates. Varenicline and bupropion are pharmacologic agents for the treatment of tobacco addiction. Smoking cessation counselling is also effective to treat tobacco addiction. It has been reported that even a 3 min counselling to a smoker enables smoking cessation rates of 5 to 10 per cent[153]. Patients with COPD who smoke and receive intensive counselling or a combination of intensive counselling and nicotine replacement therapy (NRT) or bupropion had significantly higher abstinence rates[154].

*(b) Pulmonary rehabilitation*: Pulmonary rehabilitation is an important component of therapy of COPD. The components of a comprehensive pulmonary rehabilitation programme include exercise training, smoking cessation, nutrition counselling and education. The benefits of pulmonary rehabilitation include improvement in exercise capacity, reduction in the perceived intensity of breathlessness, improvement in health-related quality of life, reduction in the number of hospitalizations and days in the hospital and reduction in anxiety and depression associated with COPD. In an evidence-based review of the literature surrounding treatment strategies for patients with COPD, pulmonary rehabilitation including at least 4 wk of exercise training is shown to cause clinically

and statistically significant improvements in health related quality of life (HRQOL) in patients with COPD and pulmonary rehabilitation also leads to a clinically and statistically significant improvement in functional exercise capacity[155]. In a randomized, double-blind, placebo-controlled trial (tiotropium, n=47; placebo, n=44), tiotropium (18 µg) administered to COPD patients participating in 8 wk of pulmonary rehabilitation (treadmill training three times a week; ≥30 min per session), it has been demonstrated that tiotropium in combination with pulmonary rehabilitation produced clinically meaningful improvements in dyspnoea and health status compared to pulmonary rehabilitation alone. Improvements with tiotropium were sustained for 3 months following pulmonary rehabilitation completion[156].

*(c) Nutritional support:* Patients from the Copenhagen City Heart Study involving 1,218 men and 914 women, aged 21 to 89 yr, with airway obstruction defined as an FEV1/FVC ratio < 0.7 were prospectively examined to know whether body mass index (BMI) is an independent predictor of mortality in subjects with COPD. This study has shown that low BMI is an independent risk factor for mortality in subjects with COPD, and that the association is strongest in subjects with severe COPD[157]. In a prospective cohort study from Korea, it has been observed that the risk of death from respiratory causes was higher among subjects with a lower BMI[158]. Survival analysis studies have shown that body weight has an independent effect on survival in COPD and the negative effect of low body weight can be reversed by appropriate therapy in some of the patients with COPD[90]. Chailleux *et al*[159] had shown that nutritional depletion was an independent risk factor for mortality and hospitalization in patients with COPD receiving LTOT and the best prognosis was observed in overweight and obese patients. European Society for Parenteral and Enteral Nutrition (ESPN)) guidelines state that enteral nutrition (EN) in combination with exercise and anabolic pharmacotherapy has the potential to improve nutritional status and function in COPD patients and frequent small amounts of oral nutritional supplements are preferred in order to avoid postprandial dyspnoea and satiety as well as to improve compliance[160]. It has been reported that nutritional supplementation may have a role in the management of COPD when provided as part of an integrated rehabilitation programme incorporating a structured exercise component as an anabolic stimulus[161]. Ghrelin is a novel growth hormone (GH)-releasing peptide that also induces a positive energy balance by decreasing fat utility and stimulating feeding through GH-independent mechanisms. Plasma ghrelin level has been shown to be decreased in COPD and this is different from other weight-loss diseases[162]. Repeated administration of ghrelin has been found to improve body composition, muscle wasting, functional capacity, and sympathetic augmentation in cachectic patients with COPD[163].

***(iv) Surgical treatment***

*(a) Lung volume reduction surgery*: The National Emphysema Treatment Trial is a randomized, multicenter clinical trial that compared lung-volume-reduction surgery (LVRS) with medical treatment. Patients with emphysema who have a low FEV1 and either homogeneous emphysema or a very low carbon monoxide diffusing capacity are at high risk for death after surgery and also are unlikely to benefit from the surgery[164]. LVRS has been shown to improve mortality, exercise capacity, and QOL in selected patients with upper lobe emphysema and poor exercise capacity. Patients with non-upper lobe emphysema and high baseline exercise capacity are poor candidates for lung-volume-reduction surgery, because of increased mortality and negligible functional gain[165]. Bilateral LVRS procedures result in greater short-term improvement than unilateral LVRS. Improvement has also been reported in dyspnoea and health status after LVRS and this is better preserved over longer-term follow up than physiological improvement. It has also been observed that physiological benefits are similar with video-assisted thoracoscopy (VATS) or median sternotomy (MS) techniques[166]. It has been reported that LVRS produces superior patient outcomes compared to medical treatment in terms of exercise capacity, lung function, quality of life and long-term (>1 yr post-operative) survival especially for patients with upper-lobe-predominant disease and low exercise capacity, but with a much greater cost per person over five years[167,168].

Alternative methods of lung volume reduction include bronchoscopic lung volume reduction and endobronchial valve placement. Endobronchial valve placement has been shown to improve lung volumes and gas transfer in patients with chronic obstructive pulmonary disease and prolongs exercise time by reducing dynamic hyperinflation[169]. Shah *et al*[170] studied lung volume reduction by placing paclitaxel-coated metal stents through bronchoscope into the emphysematous lung in a randomised trial.

This method creates a bypass allowing exhalation from hyperinflated lung regions. Though there were significant improvements in radiographic lung volume, symptoms and lung physiology on day one, the beneficial effects were not sustained and the airway bypass intervention failed to improve dyspnoea and pulmonary function at 6 months[170].

***(b) Lung transplantation:*** Lung transplantation is an option in COPD patients who have FEV1 below 25 per cent predicted and/or the $paCO_2$ is > or = 55 mm Hg. Both single- and double-lung transplant have been reported in COPD. The reported survival rates after lung transplantation are approximately 80 per cent 1-year, 50 per cent 5-year, and 35 per cent 10-year. The most important long-term complication after lung transplantation is bronchiolitis obliterans resulting in decreased pulmonary function[166]. Despite significant progress over the past 25 years, both short- and long-term outcomes remain significantly inferior for lung recipients relative to other "solid" organs[171].

### *(v) Immunization*

Vaccinations can prevent some of the infections that cause COPD exacerbations and can be administered to patients with COPD[172]. Influenza vaccination reduces lower respiratory tract infections and death in patients with COPD[173,174]. In a study of 177,120 patients with COPD (mean age 65 yr) with a mean follow up of 6.8 yr between 1988 and 2006, it had been observed that influenza but not pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD[175]. Two types of pneumococcal vaccines, polysaccharide and polysaccharide conjugated vaccines, are available. Studies have shown conflicting results with regard to the effectiveness and efficacy of the 23-valent polysaccharide vaccine. Pneumococcal polysaccharide vaccine is useful in COPD patients 65 yr and older and in younger patients with significant comorbid conditions such as cardiac disease[176,177]. However, conjugate vaccine is found to have superior immunogenicity[178]. The pneumococcal polysaccharide conjugate vaccine (PCV) comprises capsular *Streptococcus pneumoniae* polysaccharide serotypes that are individually conjugated to non-toxic diphtheria protein. Immunization with conjugated vaccines results in the development of T cell dependent immune responses, whereas unconjugated vaccines do not lead to booster responses on revaccination[179]. GOLD guidelines recommend influenza and pneumococcal vaccinations to COPD patient and state that these are more effective in older patients and those with severe disease or cardiac morbidity[7].

## X. Conclusions and future directions

The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults funded by the Indian Council of Medical Research had shown that the overall prevalence of chronic bronchitis in adults > 35 years is 3.49% (21) and this study shows that COPD is an important public health problem in India. As there are differences in clinical presentation and in the progression of disease in COPD, there is a need to understand different phenotypes in relation to clinical presentation, changes in pulmonary function, exacerbations, response to treatment and prognosis. It is increasingly realised that COPD may be due to non-smoking factors especially in our country where solid fuels are used as a source for domestic energy. The indoor biomass smoke from these sources may be an important factor causing COPD. There is a need to study the differences, if any, in pathogenesis of smoking-induced COPD and non-smoking induced COPD. The contribution of bidi smoking in causing and aggravating COPD compared to cigarette smoking is another area for future research. It has already been known that alpha-1 antitrypsin deficiency predisposes to development of COPD. Future studies including genome-wide linkage studies and other related studies may establish specific genes that contribute to the development of COPD. There is a growing realisation that COPD is a disease not confined to the lung alone, but is being recognised as systemic disease with multi-system manifestations. Better understanding of the pathogenesis in future may throw light on the consequences of COPD on other organs and new therapeutic options may emerge from the on-going studies. Globally, COPD will be the third leading cause of death by 2030[180], though COPD is a preventable disease. Therefore, urgent action is required from medical community and policy makers to reduce the burden of disease in our country by adopting appropriate preventive strategies giving due attention to COPD as is being done to diseases such as heart diseases and diabetes mellitus.

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