

Review Article

COPD Exacerbations and Respiratory Viral Infections: A PerspectiveJitender Sharma^{1*}, Roopali Rajput²¹Dept. of Biochemistry, Govind Ballabh Pant Institute of Postgraduate Medical Education & Research, Delhi -110002, India²Dept. of Biochemistry, University of Delhi, South Campus, Delhi-110021, India***Corresponding author**

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Abstract: Respiratory viruses are a major cause of concern for human population worldwide. Respiratory viral infections make it worse for patients suffering with lung diseases, such as, chronic obstructive pulmonary disease (COPD). Viral infections are one of the major inducers of COPD exacerbation. COPD exacerbations are associated with increased inflammation of the lung airways. Infection of upper respiratory tract contributes to disease progression leading to more severe exacerbation, longer duration for recovery from the disease symptoms and increased rate of hospitalization. As COPD is suspected to be one of the leading causes of mortality worldwide, this review discusses the role of respiratory viral infections in exacerbations of COPD and its immunology and genetics. Our current review presents information from articles electronically searched for keywords, such as, COPD, exacerbations, viral infections. Inclusion of articles was restricted to role of viral infections in COPD exacerbations to fulfill the relevance of the present article.

Keywords: COPD; respiratory viruses; immune system; genes; smoking.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by obstruction of airflow in lungs, airway inflammation, and decline in lung function over time, and gradual impairment in quality of life. It kills more than 3 million people each year, making it the 4th largest cause of death in the world. COPD is expected to become the third biggest cause of death by the year 2030 [1]. According to the World Health Organization, COPD kills more people than HIV-AIDS, Malaria and Tuberculosis all put together in the South East Asian region. The disease has relatively high prevalence rates worldwide (5–13%) [2, 3]. As per WHO estimates, moderate to severe COPD has been observed in 65 million people. In 2005, more than 3 million deaths across the globe were caused by the diseased condition. Data from high-income countries contributes to most of the statistics which are available on COPD burden. On the other hand, low- and middle-income countries reportedly observe about 90% of the COPD related deaths [4].

The recently updated report of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD as a common preventable and treatable disease, characterized by limitation of persistent airflow that is usually progressive and

associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [5]. COPD alone led to 2.5 million deaths in 2000 [6], 3 million in 2005 (5% death globally), and 1, 37,693 deaths in US in 2008 [7]. The prevalence of COPD in 2001 was estimated to be highest in the Western Pacific Region and lowest in Africa [8]. COPD caused 4% of all deaths in Australia in 2006 [9] and led to the loss of 47,207 years of life in 2003 [10].

High mortality and morbidity rates and a high economic and social burden caused by COPD is may be attributed to requirement for substantial and ongoing medical support [11]. In spite of availability of national and international guidelines for diagnosis of COPD, it remains considerably under diagnosed and under treated [12,13]. The current review article intends to present information relevant for an enhanced management of COPD exacerbations associated with respiratory viral infections. An electronic survey was performed for the terms, like, COPD, exacerbations, viral infections, via PubMed and Google Scholar. Cross-references were examined to include studies appropriate to the review topic.

Factors contributing to disease progression

COPD, primarily, is caused by the inhalation of toxic substances, predominantly cigarette smoking in the Western world, and indoor air pollution or particulate matter, particularly in the developing countries. There are two conditions thought to be responsible for the level of COPD severity: mucus hyper-secretion, also known as chronic bronchitis, characterized by presence of a chronic cough, and a constant increase in sputum production [14], and emphysema which is characterized by the loss of lung parenchyma and an increase in airspace size [15]. Emphysema reportedly leads to increased numbers of alveolar macrophages, neutrophils and cytotoxic T-lymphocytes which are capable of releasing a variety of cytokines and inflammatory mediators, most notably IL-8 and TNF- α [16,17]. Remodeling of the airway wall, as seen in asthma, also takes place in COPD, with differences in the anatomic sites and the structures affected.

COPD exacerbations

Many clinicians and researchers have shown substantial interest in COPD exacerbations, which are events in the natural history of COPD when the symptoms are on their high, especially those of increased dyspnea, increased sputum volume, and purulence [18]. COPD exacerbation has been reported to be an important cause of the considerable morbidity, impaired health status, and mortality [19] and has been associated with increased airway inflammation [20]. Frequent exacerbations can worsen the condition of patient and lead to faster decline in forced expiratory volume in second (FEV₁) as compared to infrequent inducers of COPD exacerbation [18, 21, 22].

Role of viruses in COPD exacerbations

Various agents have been reported to induce COPD exacerbations, viral infections being one of the most important ones [23]. Studies by different research groups demonstrate a relationship between lower respiratory tract infections in childhood and the subsequent development of chronic bronchitis and COPD [24,25]. Menezes and colleagues conducted a study involving Brazilian population and found that low family income, poor schooling, smoking, and childhood respiratory illnesses have a significant association with chronic bronchitis. Respiratory viral infections, especially rhinoviruses were reported to be a major cause of COPD exacerbations, with upper respiratory tract infections in over 50% of COPD exacerbations. More severe exacerbation and a longer symptom recovery time at exacerbation were found to be due to the occurrence of viral infection in the upper respiratory tract leading to hospitalization. The detection of respiratory viruses even during stable condition of patients, are suggestive of chronic viral infection [25].

More common occurrence of COPD exacerbations during winter season further provides evidence for induction of COPD exacerbation by respiratory viral infections [26]. However, COPD patients may also be more prone to more severe exacerbations in the winter months due to small but considerable fall in lung function with decrease in outdoor temperature [26]. Seemungal *et al.* conducted a prospective analysis of 504 exacerbations and found that the larger falls in peak expiratory flow rate were related to the symptoms of dyspnea and presence of colds and longer recovery time from exacerbations [27]. They reported in their study that up to 64% of exacerbations were associated with symptomatic colds and concluded that the exacerbations were precipitated by viruses [27]. A number of viruses which may lead to respiratory tract infections triggering the exacerbations are rhinovirus, coronavirus, influenza A and B, parainfluenza, adenovirus and respiratory syncytial virus.

Stott and colleagues reported rhinovirus infection in 14.9% exacerbations of chronic bronchitis [28]. In another study comprising 25 patients with chronic bronchitis with 116 exacerbations over a period of 4 years, researchers reported 3.4% of exacerbations due to rhinoviruses [29]. Philit *et al.* studied 35 episodes of COPD exacerbation using serology and nasal samples for viral culture. They found slight evidence for a rhinovirus etiology of COPD exacerbation [30]. In 2000, a research group attributed 27% of exacerbations in COPD patients and 44% of acute respiratory illnesses in control subjects to respiratory tract virus infections. This study in heavily influenza-vaccinated cohort identified picorna, parainfluenza and corona viruses as the most common respiratory tract pathogens [31]. Rhinoviruses, reportedly account for 43% of the virus infections in COPD patients leading to a total of about 12% of the exacerbations [31]. Seemungal and colleagues used PCR techniques for evaluation of the nature of respiratory viruses in COPD exacerbation [32]. Rhinovirus was the most common respiratory virus detected (58% of virus exacerbations), followed by coronavirus (11%), influenza (16%), parainfluenza, and adenovirus. Wilkinson *et al.* have reported that infection with two or more viruses may lead to more severe exacerbations. They found that 70% of COPD exacerbations in the UK were associated with the *Haemophilus influenzae*, and 20% exacerbations with rhinovirus [33]. In a recent study, it was found that rhinovirus was the most common causative agent, followed by coronaviruses in COPD patients (without exacerbations) in Qatar during the winter season (2008-2009) [34].

In an East London study, Rohde and colleagues speculated that the influenza immunization in 74% of the COPD patients led to relatively low levels

of virus detection. They also reported that a total of 56% of COPD exacerbations were due to respiratory virus infections out of which rhinovirus was most common (in 36% of virus-induced exacerbations) followed by influenza (at somewhat higher number at 25% of exacerbations). Since 1918, influenza A virus continues to pose severe threat among the human population [35- 37], as evident by the major outbreaks due to emerging and re-emerging virus strains. Multiple viruses were detected in 21% of COPD exacerbations in the study [38]. There has been a significant decrease in influenza-led exacerbations due to a substantial increase in influenza immunization of patients suffering from chronic lung disease. The continuous advent of novel strategies to counter the influenza A virus infection have helped in the development of effective antivirals [39-41]. However, it is still a cause of concern during influenza epidemics [42 & 43]. This has direct evidence from a study in United States, where the rate of hospitalization of non-vaccinated patients with chronic lung disease was twice during influenza season [44].

Further, influenza vaccination leads to a lower risk of death in older patients with chronic lung disease (most likely COPD) and is beneficial for the health of all patients with COPD [23]. Ko et al. reported that the most prevalent viruses detected during acute exacerbations of COPD in Hong Kong were influenza A virus [45]. In Australian community, Hutchinson and co-workers analyzed the association of respiratory virus infections with COPD exacerbations in a time-matched case-control study. Rhinovirus had the highest prevalence rate followed by influenza A virus and parainfluenza viruses, in cases with COPD exacerbations [46]. Recently, a group of researchers reported that incidence of influenza virus infection has a positive correlation with the exacerbations of COPD in Spain [47]. Influenza virus infection is the most common viral infection during acute exacerbations of COPD in South Korean population as well [48]. Geographical prevalence of viral infections during COPD is listed in the Table 1.

Table-1: Prevalence of respiratory virus infections in COPD across different geographical locations

| Geographical Region | Prevalent Virus (%age) | COPD state | Reference # |
|---------------------|-------------------------|--------------------|-------------|
| Scotland | rhinovirus (14.9) | Exacerbation | 28 |
| London | rhinovirus (58) | Exacerbation | 32 |
| United Kingdom | rhinovirus (20) | Exacerbation | 33 |
| Qatar | coronavirus (8.4) | Stable | 34 |
| East London | rhinovirus (36) | Exacerbation | 38 |
| Hong Kong | influenza A virus (5.7) | Acute exacerbation | 45 |
| Australia | Rhinovirus | Acute exacerbation | 46 |
| Asia | influenza virus | Acute exacerbation | 49 |

Torka *et al.* studied microbial patterns in 50 patients with severe COPD exacerbations. The patients were sampled for pharyngeal and tracheal aspirates, non-bronchoscopic and bronchoscopic broncho-alveolar lavage (NBBAL, BBAL) and protected specimen brush (PSB). It was found that 10% of the acute exacerbations of COPD were triggered by virus infections [49]. A study by Mohan et al showed that weighted mean prevalence of respiratory virus infections was 34.1% in acute exacerbations of COPD [50]. Influenza virus was found to be the most commonly detected virus in Asian population.

Molecular techniques for rapid detection of viruses have considerably reduced the time & effort for diagnosis of infections [50- 52]. A total of 16.2% of viruses excluding RSV were detected by PCR in patients with stable COPD; the most common being the rhinoviruses, which were found to be associated with COPD both under stable state and at exacerbation. About 7.3% and 5.9% of stable patients with COPD had

rhinovirus and coronavirus infection respectively. The presence of virus infections in stable COPD was linked to more frequent exacerbations in past one year of patient's medical history [39].

COPD Exacerbations: Immunology

The most common cause of COPD is cigarette smoke that triggers innate immunity. The stressed cells induce release of damage-associated molecular patterns which activates pattern recognition receptors (PRRs), like Toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE). This leads to release of epithelial cells, macrophages and increased expression of interleukin-1 β (IL-1 β) [53]. Autophagy is known to be the other response induced at very early stage in lung tissue of COPD patients. The increase in autophagic vacuoles, i.e. autophagosomes and autolysosomes and elevated activation of autophagic proteins, such as, Atg4B, Atg5-Atg12, and Atg7 support the occurrence of autophagy in lungs of COPD patients [54] (Figure 1).

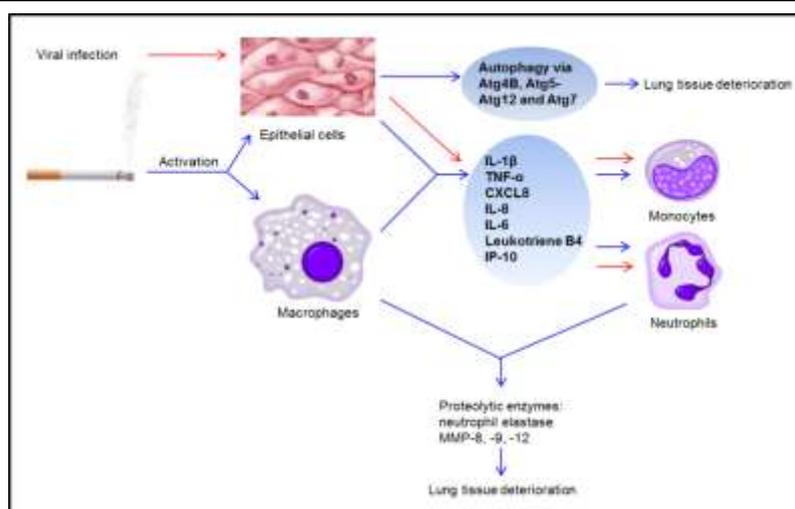


Fig-1: Immunology of lung tissue deterioration in COPD (exacerbations)

Cigarette smoke triggers release of pro-inflammatory cytokines and chemokines, viz., tumor necrosis factor- α (TNF α) and chemokine (c-x-c motif) ligand (CXCL8), from airway epithelial cells and alveolar macrophages, leading to stimulation of adhesion molecules' expression on endothelial cells and increased levels of neutrophils and inflammatory monocytes in lungs. The activated neutrophils and macrophages elicit release of oxygen radicals and proteolytic enzymes, viz. neutrophil elastase and matrix metalloproteinases (MMPs), including MMP-8, MMP-9, and MMP-12, causing deterioration of lung tissue [55, 56]. The proteolytic enzymes, perforin and granzyme B, released by CD8+ T cells and natural killer cells are also known to cause cell death by apoptosis or necrosis [57 - 59]. Histological analysis of human lung tissues from COPD patients demonstrates variations in density, morphology, and distribution of mast cell populations [59].

The adaptive immunity induced by the dendritic cells, during COPD, comprises T helper (Th1 & Th17) CD4+ T cells, CD8+ cytotoxicity, and B-cell responses. CD8+ cytotoxic T cells have reportedly been the pre-dominant T cell population in COPD patients [57 & 60]. Significant increase in the number of CD8+ T cells is known to be associated with COPD during higher stages of airflow limitation and emphysema [57]. The peripheral airways of smokers with COPD show elevated expression of chemokine receptor CXCR3 and CXCL10 [61].

COPD exacerbations have been linked with elevated expression of inflammatory agents such as, TNF- α [62], IL-8 [62 & 63], IL-6 [64], and leukotriene B4 [65], neutrophils [66] and eosinophils [66]. Papi and co-workers observed an increase in sputum eosinophils only in virus infected COPD patients with exacerbations [66]. Certain research groups have reported that virus

induced COPD exacerbations increase IL-6 and IP-10 expression [67-70] (Figure 1). However, some more studies and comparative analysis of naturally-occurring virus infections in COPD patients and non-COPD controls are necessary for making relevant conclusions on inflammatory responses to virus infection in COPD exacerbation.

COPD Exacerbations: Genetics

There is increasing evidence that genetics plays a crucial role in pathogenesis and heterogeneity of COPD [71]. The gene, *SERPINA1*, which codes α 1-antitrypsin, is found to be associated with susceptibility for COPD [72]. It has been observed that early onset of emphysema is associated with α 1-antitrypsin deficiency (AATD) [73] suggesting a possible role for its target enzymes, viz. neutrophil elastase and proteinase3. The enzymes are known to stimulate characteristic symptoms of COPD *in vivo* [74]. More recent studies involving Genome- wide association study (GWAS) link COPD with novel genetic variants, such as, 2 SNPs at *CHRNA3_5* in 15q25. *CHRNA3_5* gene encodes nicotinic cholinergic receptor α 3, 5, which is related with nicotine addiction and lung cancer [75]. *HHIP* locus on 4q31 that encodes hedgehog interacting protein (involved in regulation of morphogenesis and lung development) is also steadily linked with COPD [76]. Lung development in relation to COPD phenotypes may also be influenced by the variants of *HHIP* and *PTCHI* (encodes a membrane receptor of hedgehog protein including HHIP). High levels of expression in lungs and contribution in immune response, inflammation and tissue remodeling, highlight the significance of *AGER* or its variants in development of COPD [77]. Kong and co-researchers reported that a SNP in *BICD1* was associated with the presence or absence of emphysema in GWAS. The BICD protein is involved in functioning of dynein by interacting with dynein-dynactin [78]. Cho *et al.* demonstrated that the variants in *FAM13A* have an

association with COPD [79]. Increased mRNA levels of *IREB2* gene are found in lungs of COPD patients than the control subjects [80].

Family-based linkage analyses suggest association of *SERPINE2* in the chromosome 2q with FEV1_FVC24 and *TGFBI* in the chromosome 19q with pre-bronchodilator FEV1. *SERPINE2* codes for a 44-kDa serine protease inhibitor in cellular or extra-cellular matrix. The protein has a role in coagulation and fibrinolysis [81, 82]. Framingham and colleagues demonstrate association of FEV1 with *SMOC2* in chromosome 6q27 in general population. *SMOC2* encodes secreted modular calcium-binding protein 2 is a potential protease inhibitor owing to its homology to α 1-antitrypsin [83]. Smoking, by far, is regarded as a major cause of COPD. There are studies pointing towards the involvement of particular loci in regulating behavioral smoking. The loci influence the age to begin smoking, the frequency and the cessation of smoking. GWAS of behaviors of cigarette smoking individuals identified *CHRNA3_5* in 15q25 to be involved with smoking intensity and dependence on nicotine [84]. Ishii *et al.* recently reported the association of SNP in *SLC6A4* with COPD. The gene codes for a protein that is known to be involved in nicotine dependence trait [85]. Smoking intensity, and thereafter, development of emphysema may be attributed to deletion polymorphism of gene, *CYP2A6* that encodes a major nicotine metabolizing enzyme [86].

Different studies signify the effect of proteases like, MMPs [87], cathepsin B and collagenases [88] in induction of COPD. The oxidant-antioxidant imbalance leads to oxidative stress in body following which anti-proteases and pro-inflammatory mediators get activated [89]. It has been observed that polymorphisms in genes encoding proteases, antioxidants and inflammatory mediators [90] have an association in development of COPD features.

CONCLUSIONS

The available observations and studies point to the respiratory viral infections as the most important stimulants of COPD exacerbations. It is believed that prevention of viral infection may help in reduction of exacerbation frequency [23], thereby improving the health status of the patients. To achieve considerable decrease in COPD associated morbidity and mortality, a decline in COPD exacerbations will be very important. In developing countries of Asia, prognosis of COPD is rather worse than the developed nations, primarily owing to the poor living conditions in terms of socio-economic status, nutrition, childhood infections, environmental pollution, etc. All of these contributing to an increased rate of mortality at young ages [91]. The disease prognosis and health status of the patients have been known to improve by medications and

rehabilitation. However, termination of tobacco usage and lowering of environmental pollution are central to achieve effective prevention and apprehension of COPD development. Therefore, it is the need of the hour to focus on the often missed out factors and follow a specified approach including patient specific therapies, for its better management and control.

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