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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND ITS ASSOCIATION WITH INTERLEUKIN 1 BETA: AN UPDATE

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Abstract

The third greatest cause of mortality worldwide is Chronic Obstructive Pulmonary Disease (COPD), a progressive and long-term illness that obstructs airways. Genetic and environmental variables both have an impact on COPD. COPD patients' lungs and airways have a chronic inflammatory response that is brought on by smoking, biomass smokes, home pollutants, etc. These trigger neutrophils and macrophages resulting in release of various cytokines along which, the proinflammatory cytokine IL1β is the most frequently found innate immune cytokine associated with COPD. In this review we are discussing the variations in the association of serum levels of IL1β in COPD and also in the polymorphism of IL1β in COPD patients.

INTRODUCTION

COPD is a heterogeneous lung condition characterized by persistent respiratory conditions (cough, production of sputum, dyspnea) caused by abnormalities of the airways (bronchitis, bronchiolitis), alveoli (emphysema), and/or both that result in persistent, often progressive airflow obstruction [1]. The estimated global age-standardized prevalence of COPD ranging from 2% to 5% in different years, the global burden of disease (GBD) estimates the prevalence of COPD in 328 million people in 2010 (4.77%), 299 million in 2017 (3.9%), and 212 million in 2019 (2.7%) [2]. COPD accounted for 3.23 million deaths in 2019, ranking it as the third most common cause of death globally [3]. COPD cases in India was estimated to be 55.3 million in 2016 [4]. Based on available data, it appears that men are more likely than women to have COPD. The ratios of men and women are beginning to equalize, though, according to a new trend that has emerged. The growing number of female smokers is the cause of this [5]. It's probable

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that cytokines are crucial in this disease because COPD is closely associated with a common chronic inflammatory process, which includes tissue damage and healing. The primary cytokine responsible for inducing inflammatory responses in COPD patients is believed to be IL1β [6]. It has been demonstrated that in the Japanese, Egyptian, Caucasian, and Indian populations, neither of the genotype distributions of the polymorphism IL-1β (-511 C/T) is related to the decrease of rate function in lung or in developing COPD. In contrast, according to Lee et al., polymorphism in IL-1β (-511 C/T) significantly increased the risk of COPD in the Korean population [7].

COPD

A chronic condition characterized by progressive airflow limitation and tissue destruction known as COPD. Cigarette smoking is linked to COPD as the main cause. Chronic inflammation causes airway constriction and decreased lung recoil, which can progress from being asymptomatic to respiratory failure. Alpha-1 antitrypsin deficiency (AATD), exposure to the environment and at work place, and secondhand smoke are possible additional causes.

AAT (Alpha-1 antitrypsin) is a protein made in the liver, deficiency of AAT in the liver, is the cause of AATD. When COPD patients show signs of liver damage, AATD should be suspected, lower lobes are mostly affected in AATD [7]. The inflammatory response and airway blockage lower the forced expiratory volume (FEV1), tissue destruction which results in poor gas exchange and restricted airflow. Imaging tests often reveal hyperinflation of the lungs during exhalation due to air trapping from the collapsed airway. The inability to completely exhale also contributes to an increase in carbon dioxide (CO2). As the disease progresses, impaired gas exchange is often seen. Retention of CO2 caused by an increase in physiologic dead space or a decrease in ventilation. Pulmonary hypertension may arise from diffuse vasoconstriction brought on by hypoxemia [8,9].

Chronic bronchitis (CB) and emphysema are the two main causes of COPD [10].

A productive cough lasting longer than three months and returning more than twice a year is the classic indicator of CB. Symptoms of chronic bronchitis typically include tiredness, a persistent productive cough, stomach ache, and/or chest pains. Individuals with chronic bronchitis may experience recurrent exacerbations of the illness in addition to a rise in sputum volume, purulence, or both [11]. Patients with CB therefore experience symptoms like chronic cough, phlegm production, and shortness of breath [12].

Lung emphysema a condition in which, the alveolar walls are irreversibly destroyed, which causes the distal airspaces to expand. Emphysema does not cause fibrosis at first, but end-stage emphysema can cause a reparative reaction that eventually results in lung fibrosis. Pulmonary emphysema occurs in three forms: Septal emphysema (I), centri lobular (II), and pan lobular. Moreover, pulmonary emphysema's severity and distribution can reveal information about its etiology: Smoking-related emphysema often affects the higher lung parts, whereas lung emphysema originating from AATD is situated in the basal lung sections [13].

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Depending on the Global Burden of disease region, different percentages of COPD-related DALYs (Disability Adjusted Life Years) were associated with different risk factors. Smoking (46.0%), workplace gases, fumes, particulate matter (15.6%) and ambient particulate matter pollution (20.7%) were the main causes of DALYs from COPD globally.

Men had a larger percentage of DALYs from COPD that could be linked to these three causes. The percentage of COPD-related DALYs owing to specific causes varied by age group as well. Up to the age of 70–74, the percentage of smoking-related DALYs rose; after that, it started to decline.

While the 65–69 age group had, the highest associated DALYs due to ambient particulate matter pollution. Moreover, the age group of 70–74 exhibited the largest percentage of DALYs associated with COPD due to occupational exposure to gases, fumes, and particulate matter [14].

Many questions are typically asked for the diagnosis, such as whether the patient smokes or has ever smoked, if they have been exposed to lung irritants at work or in the past, if they have been exposed to a lot of secondhand smoke, and if there is a family history of COPD. Spirometry is a non-invasive test used to evaluate lung function.

Treatment can reduce the advancement of the disease, avoid complications, and improve symptoms. Physical and respiratory therapists as well as lung specialist (pulmonologist) may be of help [15].

In addition to COPD, managing chronic conditions is crucial, especially diabetes mellitus and heart disease [16].

World Health Organization (WHO) examined fatalities in a multicenter COPD patient study and gathered information from 215 individuals with severe COPD and persistent respiratory failure who passed away after receiving long-term oxygen therapy. In the hospital, 75% of patients passed away. Respiratory failure was the primary cause of mortality in this critically ill group of COPD patients [17].

Pathophysiology of COPD

The pathophysiology of COPD has long been thought to involve persistent inflammation of the lung parenchyma and airways. Certain inhaled irritants, including cigarette smoke, activate macrophages, neutrophils and CD8+ T lymphocytes, these cells subsequently produce a range of mediators. These inflammatory processes cause parenchymal damage and airway remodeling, which obstruct airflow [18]. Many T-cell, chemokines, growth factors and pro-inflammatory cytokines have been linked to the pathophysiology of COPD. IL-1β and TNF-α both induce inflammation, which exacerbates COPD [19]. In immune system regulation and inflammation modulation cytokines and interleukins play a role. The association between variations in interleukin coding genes, such as IL1A, IL1RN, IL1β, IL4, IL8, IL6, IL10, IL12, IL13, IL17, IL18, and IL27, and COPD susceptibility has been the subject of numerous genetic epidemiology research, however their conclusions have been inconsistent [6].

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One cytokine that has a broad range of physiological and biological impacts is IL-1, which acts as an interleukin trigger to release a series of pro-inflammatory cytokines. The biological action of IL-1 is associated with the activation of nuclear transcription factors NF-kB and AP-1, which in turn stimulates the synthesis of several molecules involved in the regulation of the inflammatory response [20].

Role of cytokines in COPD

Small secreted proteins (less than 40 kDa) called cytokines are produced by nearly all cells and have a role in immunological response and control. Pro-inflammatory cytokines will cause the immune system to get activated, produce more cytokines, and release more of them. However, current studies show that any immune response requires the simultaneous release of anti- and pro-inflammatory cytokines.

The so-called superfamilies that make up cytokines do not always describe shared genes; rather, they describe structural similarities. Furthermore, distinct cell groups can produce the same cytokine. Because cytokines' actions vary according to the targeted cell, they are pleiotropic. Also, distinct cytokines could be redundant because they have the same impact. Still, there's a chance they work in concert. Lastly, they may initiate signaling cascades, which means that even minute quantities of protein may have disastrous effects [21].

The IL-1 family includes IL-1β, IL-1α and IL-1 receptor antagonist (IL-1RN). A key participant in cellular processes such cell differentiation, inflammatory response, and apoptosis is IL-1β [7]. IL1β belongs to the IL-1 family and exhibits a wide range of biological effects that can be both beneficial and harmful [22].

The liver produces acute phase proteins in response to IL-1 such as, C-reactive protein (CRP) and in people with COPD, CRP is associated with a lower level and a faster decline in lung function. The most effective indicator for bacteria, viruses, or sputum eosinophilia-related COPD exacerbations has been demonstrated to be sputum IL1β, which is a well-known factor for a decline in lung function [23].

The polymorphism of the interleukin-1 (IL-1) gene cluster is linked to a number of inflammatory illnesses and involved in the regulation of the synthesis IL-1 receptor antagonist (IL-1RA) and IL-1. By attaching itself to the IL1 receptor, interleukin-1 receptor antagonist (IL1RN) inhibits IL1β competitively. Additionally, it has been demonstrated that a cigarette dose-dependent rise in IL1β is seen in the Broncho alveolar lavage fluid of chronic smokers [24].

IL-1β and IL-1α in the lung are essential for the immune system's protection against inhalation of several toxic substances, such as particulate matter, cigarette smoke, and nanoparticles (silica and titanium dioxide). Data from an acute silica exposure mouse model show that IL-1 is generated early in the lung to support the inflammatory response. In this instance, IL-1α was released during the initial hours and reaches its peak 6 to12 hours later, inducing the production of inflammatory mediator, such as IL-1β 24 hours later [25].

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In COPD, a major role in inducing neutrophil airway inflammation is IL1β, mostly through the following mechanisms: IL1β is a strong inducer of IL-8 and IL-6 in normal human bronchial epithelial cells. These two cytokines aid in the respiratory tract's neutrophil recruitment and activation [26].

Cyclooxygenase-2 and prostaglandin E2 are both induced by IL-1β in human lung fibroblasts, and both substances at high and low concentrations prevent enhanced fibroblast proliferation. However, fibroblast proliferation is increased by IL-1β at modest dosages, indicating a concentration-dependent biphasic effect of IL-1β-induced lung fibroblast proliferation [27].

Furthermore, IL1β increases bronchoalveolar lavage fluid in pulmonary inflammation caused by chronic cigarette smoking and increases dendritic cells and T-lymphocytes in lung tissues [28]. The human IL1β gene loci are located on chromosome 2q14 in a cluster. The IL-1 gene complex contains a number of known common polymorphisms, such as the single nucleotide polymorphisms (SNPs) in IL1β at position -511 (rs16944) [29]. Apart from causing local airway inflammation, by increasing IL1β can be seen in systemic inflammation possibly due to spillover from the lung into systemic circulation, can link between COPD and comorbidities [28].

To evaluate the association between IL1β and COPD several studies have been conducted. The IL1β -511 (rs16944 C/T) single nucleotide polymorphism and serum IL1β levels in COPD have been the focus of studies, but they had inconsistent results. Xie Z-K, et al (2014) found that, tumor necrosis factor-α (TNF-α), IL-6, IL-8, and other inflammatory mediators are just a few of the inflammatory mediators that are induced to express; other inflammatory mediators that are regulated by IL-1β include the differentiation of inflammatory cells and the movement of inflammatory cells from the blood to inflamed tissues.

Since IL-1β controls several inflammatory processes, changes in its blood or tissue levels can have a substantial impact on these processes compared to (-511) C and (-31) T alleles, which are linked to lower levels of IL-1β, the IL1β (-511) T and (-31) C alleles are related with higher amounts of IL-1β and with severe inflammation. Genetic variation in the IL1β gene's level of expression may change a person's vulnerability to COPD, the study reported in East Asians, the IL1B (−511) polymorphism is related to COPD risk [25]. Zou Y, et al (2017) found that, IL-1β was responsible for the initiation and maintenance of neutrophil airway inflammation in patients with COPD.

This was primarily due to two mechanisms: first, IL-1β stimulated the production of numerous inflammatory cytokines by normal human bronchial epithelial cells, including IL-6 and IL-8, which are thought to promote neutrophil recruitment and activation; second, IL-1β could increase the number of T lymphocytes (αβ T cells and γδ T cells) in the lung, thereby promoting the expression of IL-17. IL-17 was identified as a crucial regulator of neutrophils.

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Neutrophils thus have a role in the production of IL-1β, which promotes the recruitment of neutrophils into airways and sets off a vicious cycle of neutrophil airway inflammation that ultimately leads to the gradual development of COPD, the study reported, elevated serum levels of IL-17 and IL-1β could be employed as a biomarker to detect ongoing neutrophilic airway inflammation and possible COPD exacerbation [28]. Ahmadi A, et al (2019) found that, the interleukin 1 cytokine family includes a protein that is encoded by the IL-1 Antagonist Receptor (IL1RN) gene.

On the activities of both IL-1α and IL-1β, this protein has detrimental regulatory effects. Furthermore, IL1RN is highly significant in IL1-induced inflammatory reactions. A typical feature of the pathophysiology of COPD is tissue damage caused by aberrant inflammatory activity caused by IL-1 dysregulation, the study reported no significant association between IL1β (rs16944) gene and COPD [6]. Baykara O, et al (2017) carried out a haplotype analysis for the polymorphisms -511 C > T and +3954 C > T; however, no significant link was found since the haplotype frequencies of CT, CC, TC, and TT were close to one another.

These inconsistent findings may be partially explained by racial disparities in various environmental settings. Pathogen-associated molecular pattern molecules (PAMPs) or damage-associated molecular pattern molecules (DAMPs) are stimulated to generate and release IL-1β.

Although the specific method of secretion is unknown, there are a number of release mechanisms. Generally speaking, IL-1β is secreted by monocytes, macrophages, and dendritic cells, the study reported no association between COPD and IL1β gene polymorphism [7]. Budi Mulya N, et al (2021) results are supported by research of Amer and Sapey. Sapey et al. Amer and Sapey's research supports the findings. According to Sapey et al., there was no discernible variation in serum IL-1β levels between those with COPD and those in good health.

On the other hand, he discovered a considerable decrease in the expression of cytokine antagonists (IL-1RA and IL-1R2) against IL-1β. He takes into account the decline in IL-1β antagonistic influence on pro-inflammatory activity, which leads to inflammation and eventually COPD, the study reported no correlation between serum level of IL1β and COPD [5].

CONCLUSION

We concluded that IL1β has a major role in airway inflammation, IL1β also increases T-lymphocytes and dendritic cells in lung tissues in chronic cigarette smoking induces pulmonary inflammation and therefore it has been implicated in the pathogenesis of COPD. Variations in the association of serum levels of IL1β in COPD and also in the polymorphism of IL1β in COPD has been seen. From various studies we got inconsistent findings, therefore more studies in area of IL1β in association with COPD is essential.

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SUMMARY

Study	Significance
Ahmadi A, et al (2019)	Their results suggest that in Caucasian and Asian populations, IL1β-rs16944 may not be a substantial risk factor for COPD development.
Baykara O, et al (2017)	The study's findings show that in the Turkish population, there is no association between the IL1β-511 polymorphism and COPD.
Shyam Prasad Shetty B, Chaya SK, et al (2021)	The study found that IL1β and TNF-α were raised in COPD patients, suggesting that these two factors could be helpful indicators of the illness and the severity of airway limitation.
Shukla RK, Kant S, et al (2012)	The genotype frequencies of IL1B polymorphisms T (-511) C in people with COPD do not significantly differ from one another, according to the study.
Xie Z-K, Huang Q-P, et al (2014)	The study's findings suggest that there is a correlation between the risk of COPD and the IL1B (−511) polymorphism in East Asians.
Zou Y, Chen X, et al (2017)	The study suggests that increased serum IL1β and IL17 levels could be used as a biomarker to detect COPD and persistent neutrophilic airway inflammation.
Budi Mulya N, Ilyas M, et al (2021)	According to the study no correlation was seen between serum level of IL1β in COPD.
Ishii T, Matsuse T, et al (2000)	The investigation found no connection between COPD and the IL1β polymorphism.

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