

## Inflammation and oxidative stress in COPD

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### Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic lung problem that needs higher attention. Smoking and pollution are main causative agents of this health problem. Inflammation and Oxidative stress are the major markers of COPD and antioxidant enzyme status can be used as biomarker to assess various chronic diseases. Antioxidant defense system plays an important role to control oxidative stress caused by free radicals and other reactive species (reactive oxygen species and reactive nitrogen species). In COPD subjects, permanent oxidative stress continuously produced in the body caused imbalanced response of endogenous antioxidant enzyme. So, this disease is major public health problem and life threatening. This is the time to generate some treatment and drugs to prevent and cure the chronic lung disease.

**Keywords:** COPD, Oxidative stress, Inflammation

### Introduction

Chronic obstructive pulmonary disease (COPD), a chronic lung condition is characterized by the presence of chronic bronchitis or emphysema that may result to the obstruction in airways (MacNee, 2006) [10]. It is currently largest and major health problem and the fourth leading cause of worldwide mortality, predicted to become the third by 2030 (McGuinness and Sapey, 2017) [11].

There are various important risk factors of COPD progression. First, Smoking has been known to be major risk factor of COPD accounting to almost 85% of the COPD cases (50% smokers develop COPD) the remaining 15% classified as non-smoking COPD (Mannino *et al.*, 2006; Mannino and Buist, 2007) [9, 8]. This estimated data was generated from very few number of studies conducted only in developed countries. Second, Long exposure (at least 25 years) to indoor air pollution from partial combustion of biomass fuel for cooking and other purposes in poorly ventilated homes. Another Major cause for non-smoking COPD is the prolonged exposure to occupational smoke/dust e.g. metal etching, food product manufacturing, rubber products, chlorinated organic compounds dyes, explosives etc. Along with these risk factors, outdoor air pollution, poor nutrition, female gender, genetic and old age are also causes of this chronic disease (Brashier and Kodgule, 2012) [3].

### Molecular mechanism involved in COPD pathogenesis

COPD primarily affects the small airways and alveoli of the airways. There are two major important mechanism played role in the pathogenesis of COPD. First, the presence of inflammatory cells / molecules and disturbed balance between oxidant-antioxidant leading to oxidative stress (MacNee, 2006) [10]. Neutrophils, macrophages and lymphocytes are cells primarily involved in COPD inflammation. Inflammatory molecules released by inflammatory cells like chemokines, cytokines and chemoattractants which causes inflammation through uncontrolled cascade. Neutrophils further attract other neutrophils at the inflammation site by

releasing chemoattractants like interleukin-8 (IL-8) and leukotriene (Stockley, 2002) [18]. Neutrophils release various proteolytic enzymes proteinase-3, Elastase cathepsin G, cathepsin B and matrix metalloproteinases (MMP) cause damage to elastic lung tissue. Besides this process, macrophages also release cytokines such as IL-8, IL-6, IL10 TNF- $\alpha$ , LTB4 etc. Reactive oxygen species (ROS) attract and activate various inflammatory cells, and particularly MMPs family members such as MMP-2, MMP-9, MMP-12, MMP-14 and elastolytic cysteine proteinases such as cathepsin K, L and S (Tetley, 2002) [19]. CD4 Lymphocytes has been known to induce autoimmune response to the lung tissue for self-killing process. other destructive enzymes such as perforin and granzyme B released by CD8+ lymphocytes which can induce apoptosis of the alveolar epithelial cells (Barnes and Cosio, 2004) [2]. All this series attributed to oxidative stress such as oxidative inactivation of antiproteases and surfactants, membrane lipid peroxidation, alveolar epithelial injury and apoptosis, reduction in elastin collagen synthesis and fragmentation of these skeletal proteins. Overall, this complete story revolves around oxidative stress, inflammation and pathogenesis of COPD.

### Proofs for link between oxidative stress and COPD

Various parameters/methods such as Exhaled breath condensate (EBC), FRAP assay, catalase activity, immunohistological staining and other enzymatic assay have been used to assess the presence of oxidative stress in the lungs of COPD patients, and there is proof of an increased oxidative burden in COPD compared with controls (McGuinness and Sapey, 2017) [11].

Exhaled breath condensate (EBC) is very effective method used to find oxidative stress products (markers) in the lungs (Horvath *et al.*, 2005). As reported in literature that H<sub>2</sub>O<sub>2</sub> has found significantly increased in the exhaled breath condensate of COPD subjects compared to healthy controls (Dekhuijzen *et al.*, 1996) [4] (Nowak *et al.*, 1999) [14]. Arachidonic acid is a polyunsaturated fatty acid found in cell membranes in

abundance, peroxidised to form isoprostanes by free radicals in vivo, (Morrow *et al.*, 1990) which can be measured in EBC and have been found to be increased in COPD (Montuschi *et al.*, 2000) [12]. Malondialdehyde (MDA) product of lipid peroxidation (LPO) was also found to be significantly higher in the EBC of 73 COPD subjects as compared to healthy controls. This study also proved that MDA levels are inversely with forced expiratory volume in 1 second (FEV<sub>1</sub>) in COPD patients (Bartoli *et al.*, 2011) [1].

MDA and GPx activity in serum correlate with COPD severity, with increased serum MDA and decreased GPx correlating with increased COPD severity when compared with healthy non-smokers (Kluchova *et al.*, 2007) [7].

Immunohistological staining also used to assess the oxidative stress level in COPD cases, it is used to visualise some oxidative stress products within distinct cellular components of the lung e.g. 4-hydroxy-2-nonenal (4HNE), a product of lipid peroxidation readily forms adducts with several protein residues. Nitrotyrosine and inducible nitric oxide synthase (iNOS) are markers of nitrogen derived oxidative stress which is found to be increased in COPD correlating inversely with FEV<sub>1</sub> (Ichinose *et al.*, 2000) [6] (Ricciardolo *et al.*, 2005) [15].

The FRAP assay measures the formed ferrous ions by increased absorbance. The assay determines the antioxidant activity in the micromolar range needing minutes to hours (Schlesier *et al.*, 2002). Sochor *et al.* (2010) [17] observed the behaviour, kinetics, time courses and limitations of the fully automated spectrometric method for FRAP assay. Nadeem *et al.* (2005) [13] observed that the total antioxidant power of plasma, measured as its ferric reducing ability, was significantly reduced in COPD patients as compared to the healthy non-smoking controls. Recently Singh and Yadav (2016) [16] have also reported significantly lower mean value of total antioxidant ability in COPD patients as compared to controls.

### Conclusion

Tobacco smoking leads to oxidative DNA damage and contributes to the pathogenesis of COPD. Various sources of DNA damaging reactive species include oxidants present in cigarette smoke, infiltration of ROS generating inflammatory cells and enzymes, and oxidants generated as second messengers in signalling mechanism. There are no clinically available drugs and treatments that can cure and prevent COPD progression. So, there is huge scope and opportunity to work in that area in prevention of COPD.

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