شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

شبكة المعلومات الجامعية
التوثيق الالكتروني والميكروفيلم

HANAA ALY

شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, and is predicted to be the third-leading cause of death worldwide by 2020 ***(Global Initiative for Chronic Obstructive Lung Disease, 2017)***. COPD is characterized by persistent, progressive airflow limitation associated with chronic inflammation that is responsible for permanent structural changes to the airway and lungs. These include airway narrowing due to increased wall thickness, mucus occlusion, and destruction of lung parenchyma with loss of lung elasticity ***(Kim et al., 2008)***. Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, with patients displaying varying clinical and pathophysiological features. The identification of COPD phenotypes with distinct characteristics may allow targeted treatment strategies directed towards specific biological pathways.

Eosinophilic COPD appears to be a distinct patient subgroup with a corticosteroid treatment response Furthermore, some, but not all, studies have shown that higher blood eosinophil counts in COPD patients predict a higher exacerbation rate in the future ***(Singh et al., 2014; Vedel-Krogh et al., 2015).***

The prevalence of eosinophilia in COPD patients varies depending on the threshold used for evaluation. In a metaanalysis of ten trials, 63% of patients (n=10,861) had blood eosinophil counts >2% ***(Pavord et al., 2016)***. The detection of elevated eosinophil concentrations and eosinophil-associated proinflammatory factors in the airways and blood of patients with COPD suggests that eosinophils actively contribute to inflammatory processes in these patients. A growing body of evidence supports an association between high eosinophil concentrations and exacerbations of COPD ***(Saha and Brightling, 2006; Bafadhel et al., 2011; Vedel-Krogh et al., 2016; Siddiqui et al., 2015; Price et al., 2014).*** Some studies have noted greater eosinophil counts during exacerbations compared with periods of stable disease, while others have reported an association between greater eosinophil counts and an increased exacerbation risk ***(Cheng and Lin, 2016)***.

Acute exacerbation of COPD significantly increases symptoms, deteriorates pulmonary function, increases rate of hospitalization and lengthens hospital stay further impairing functional capacity and quality of life (QOL) imposing additional burden to healthcare system ***(Bafadhel et al., 2012; Brightling et al., 2005; Barnes et al., 2016).*** The in-hospital mortality can reach 30% or more ***(Bafadhel et al., 2012)***. Seeking for predictive biomarkers for clinical outcome in this population is thus of high priority.

Numerous studies have evaluated eosinophilia in relation to exacerbation risk ***(Negewo et al., 2016; Vedel-Krogh et al., 2016; Pavord et al., 2016)*** length of hospital stay ***(Salturk et***

al., 2015; Serafino-Agrusa et al., 2016; Duman et al., 2015), in-hospital mortality and response to steroidal and bronchodilator therapies ***(Barnes et al., 2016)*** but the evidence is conflicting. Some studies have reported a higher risk for exacerbation in patients with eosinophilic COPD ***(Pavord et al., 2016).*** Conversely, a retrospective study suggested that a higher level of eosinophils protected against disease aggravation ***(Duman et al., 2015)***.

Across several studies, elevated eosinophil concentrations have been found to predict response to ICS in patients with COPD ***(Hinds et al., 2016; Barnes et al., 2016).*** In patients with blood eosinophil counts of >2%, ICS–LABA has significantly reduced exacerbation rates compared with placebo (P=0.001) Trial of Inhaled Steroids And Long-Acting β2 Agonists [TRISTAN] study) and with tiotropium (P=0.006; Investigating New Standards For Prophylaxis in Reducing Exacerbations [INSPIRE] study) ***(Pavord et al., 2016)***. In contrast, there were no significant differences in exacerbation rates between treatments in patients with blood eosinophil counts <2% in either study.

Other research teams failed to detect any association Evaluation of ICS efficacy for treating exacerbations in COPD patients with elevated eosinophil counts supports an association between eosinophils and exacerbations, although results between studies are conflicting. ***(Cheng and Lin, 2016)*** found in a post hoc analysis of 248 patients with COPD treated with medium-or high-dose ICS in combination with a LABA. that a higher percentage of patients with baseline (prerandomization) blood eosinophil counts >3% had a history of acute exacerbations with >1 hospitalizations in the prior year (before study start) compared with patient baseline blood eosinophil counts ≤3% (27.1% vs 7.4%, respectively) ***(Cheng and Lin, 2016)***.

IL5 is one of the major cytokines involved in eosinophil-mediated inflammation: it promotes the differentiation, survival, trafficking, activation, and effector functions of eosinophils. Migration of eosinophils to the lungs is controlled by specific chemotactic factors, such as CCL5 (RANTES), CCL7 (MCP3), CCL11 (eotaxin 1), CCL13 (MCP-4), CCL15, CCL24, and CCL26 acting on the CCR3, along with CRTH2, which is expressed on T-helper 2 cells and its ligand, prostaglandin D2. Once in the lungs, proinflammatory mediators, including basic proteins (major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin), cytokines (IL2, IL3, IL4, IL5, IL10, IL12, IL13, IL16, IL25), chemokines (CCL5, CCL11, CCL13), and growth factors (tumor necrosis factor [TNF], transforming growth factor [TGF]α/β), that are released by eosinophils contribute to sustained inflammation and tissue damage ***(Tashkin and Wechsler, 2018)***.

AIM OF THE WORK

To assess the prevalence of eosinophilic COPD and their clinical characteristics in COPD patients

Chapter 1

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Definition:

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases ***(GOLD, 2019).***

The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person ***(GOLD, 2019).***

Epidemiology:

Prevalence:

Chronic obstructive pulmonary disease (COPD) is the fourth major cause of mortality and morbidity and suspected to rise to third soon as our efforts to prevent, identify, diagnose and treat patients at a global population level have been insufficient ***(Ho et al., 2019).***

It is estimated that chronic obstructive pulmonary disease (COPD) affects 210 million people worldwide ***(Hawkins et al., 2015).***

More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. COPD represents an important public health challenge that is both preventable and treatable. COPD is a major cause of chronic morbidity and mortality throughout the world ***(GOLD, 2019).***

The number of deaths is projected to increase further because of higher smoking rates in the developing world, and an aging population in many countries. It resulted in an estimated economic cost of $2.1 trillion in 2010 ***(Lomborg, 2013).***

Age:

- It typically occurs in people over the age of 40 ***(Georgios et al., 2018).***

Sex:

- Males and females are affected equally commonly ***(Georgios et al., 2018).***

Predisposing factors:

Tobacco smoking

- It is the most common cause of COPD ***(Decramer et al., 2012).***
- Tobacco smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in forced expiratory volume in the first second(FEV1), and a greater COPD mortality rate than non-smokers. Other types of tobacco (e.g., pipe, cigar, water pipe) and marijuana are also risk factors for COPD ***(Yin et al., 2007).***

Indoor air pollution

- The results of burning of wood and other biomass fuels used for cooking and heating in poorly vented dwellings, is a risk factor that particularly affects women in developing countries ***(Eisner et al., 2010).***

Occupational exposures

- Organic and inorganic dusts, chemical agents and fumes, are under-appreciated risk factors for COPD ***(Eisner et al., 2010)***

Outdoor air pollution

- It contributes to the lungs' total burden of inhaled particles, although it appears to have a relatively small effect in causing COPD ***(Eisner et al., 2010).***

Genetic factors

- Severe hereditary deficiency of alpha-1 antitrypsin (AATD) 15; the gene encoding matrix metalloproteinase 12 (MMP-12) and glutathione S-transferase have also been related to a decline in lung function or risk of COPD ***(Gershon et al., 2011).***

Age and sex

- Aging and female sex increase COPD risk ***(Gershon et al., 2011).***

Lung growth and development

- Any factor that affects lung growth during gestation and childhood (low birth weight, respiratory infections, etc.) has the potential to increase an individual's risk of developing COPD ***(Gershon et al., 2011).***

Socioeconomic status

- Poverty is consistently associated with airflow obstruction ***(Eisner et al., 2010)*** and lower socioeconomic status is associated with an increased risk of developing COPD. It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition, infections, or other factors related to low socioeconomic status ***(Gershon et al., 2011).***

Asthma and airway hyper-reactivity

- Asthma may be a risk factor for the development of airflow limitation and COPD ***(Gershon et al., 2011).***

Chronic bronchitis

- Chronic bronchitis may increase the frequency of total and severe exacerbations ***(Kim et al., 2011).***

Infections

- Severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood ***(McGuinness et al., 2017).***

Pathogenesis:

- In healthy lungs, antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase, provides an endogenous biological defense against oxidative stress caused by cigarette smoking ***(McGuinness and Sapey, 2017).***

- An imbalance between the oxidants and antioxidants leads to increased expression of genes involved in inflammation, increased secretion of airway mucus, and inactivation of anti-proteases ***(McGuinness and Sapey, 2017).***

- Inhaled particles and pathogens are recognized with pattern recognition receptors (PRRs) on the plasma membrane of the alveolar epithelial cells and macrophages ***(McGuinness and Sapey, 2017).***

- There are several types of PRRs: toll-like receptors, cytosolic NOD-like receptor (NLRs), and RIG-I-like receptors ***(McGuinness and Sapey, 2017).***

- PRRs are activated by damage-associated molecular patterns (DAMPs) released after tissue damage, resulting in the production of inflammatory cytokines and the formation of the nucleotide-binding oligomerization domain like receptor (NLR) P3 inflammasome ***(McGuinness and Sapey, 2017).***

- NLRP3 inflammasome leads to the secretion of interleukin (IL)-1α, IL-1β, IL-33, and IL-18.

- IL-1β and IL-18 activate neutrophils, macrophages, helper T (Th) 1, and Th17 lymphocytes leading to airway inflammation ***(McGuinness and Sapey, 2017).***

- Alveolar macrophages and neutrophils release proteases, such as matrix metalloproteinase (MMPs) and neutrophil elastase, which cause elastin degradation that results in alveolar wall destruction promote mucus production in the submucosal glands and goblet cells ***(Barnes, 2016).***

- Antigens released by cell and tissue injury are recognized by the dendritic cells and presented to T-lymphocytes to generate Th1 and Th17 ***(Barnes, 2016).***
- In healthy subjects, regulatory T (Treg) cells, M2 macrophages, and myeloid-derived suppressor cells create immune tolerance that suppresses that process, This process is impaired in COPD ***(Barnes, 2016).***
- CD8-positive cytotoxic T lymphocytes and CD4-positive Th1 lymphocytes as well as natural killer cells release perforin and granzyme B to induce alveolar destruction ***(Barnes, 2016).***

All this leads to:

1) Impaired epithelial function and shortening of the cilia on the epithelium.
2) Goblet cell hyperplasia and mucous hypersecretion due to the reduction in mucociliary clearance.
3) Extracellular matrix degradation (especially degradation of lung elastin).