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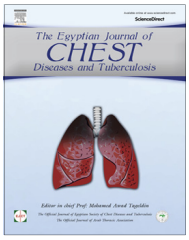

ORIGINAL ARTICLE

The impact of smoking on inflammatory biomarkers in patients with chronic obstructive pulmonary disease

Yasser A. Korani [a], **Alaa T. Hassan** [a,*], **Effat A.E. Tony** [b], **Madleen Adel A. Abdou** [c]

[a] *Departments of Chest, Faculty of Medicine, Assiut University, Assiut, Egypt*
[b] *Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt*
[c] *Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt*

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KEYWORDS

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Abstract *Background:* Chronic obstructive pulmonary disease (COPD) is a chronic progressive inflammatory disease characterized by airflow limitation that is not fully reversible (Nillawar et al., 2012). The pathophysiology of COPD is not completely understood. Cigarette smoking is a major risk factor for chronic obstructive pulmonary disease (COPD). Elevated CRP has been increasingly used as a surrogate marker of systemic inflammation in diverse conditions. TNF-α, a powerful pro-inflammatory cytokine primarily produced by activated macrophages, is thought to play a critical role in the pathogenesis of COPD (Higashimoto et al., 2008; Churg et al., 2002).

The aim of the work: To evaluate the impact of smoking on inflammatory biomarkers and relations between these biomarkers and the decline of lung function in COPD patients.

Methods: This case–control observational prospective study was conducted on fifty-eight clinically stable COPD patients (26 non-smokers and 32 current smokers; at different stages ranged from mild to very severe), their mean age 53.1 ± 14.25 and 53.9 ± 5.95 years respectively), recruited from Chest Department, Assiut University Hospitals. All patients met the Global Initiative for Obstructive Lung Disease (GOLD) (Battaglia et al., 2007). All participants were subjected to thorough history taking, full clinical examination, anthropometric measurements with spirometry and chest X-ray. Peripheral hemogram, liver function tests, kidney function tests, high sensitivity C-reactive protein (hs CRP) and serum level of TNF-α were measured for both patients and controls.

Results: The concentrations of circulating hs-CRP and TNF-α, were highly significantly elevated in patients with COPD in comparison to the control group (3.74 ± 0.2 vs. 1.30 ± 0.14 for hs-CRP;

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; Hs-CRP, highly sensitive C-reactive protein; FEV1, forced expiratory volume in one second; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; BMI, body mass index; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IL, interleukin; SpO_2, peripheral oxygen saturation; TNF-α, tumor necrosis factor alpha.

* Corresponding author.
E-mail address: alaathabet35@yahoo.com (A.T. Hassan).

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33.88 ± 5.97 vs. 8.79 ± 0. 57 for TNF-α with $p < 0.0001$ for each) and the levels of measured TNF-α were significantly increased with the increased degree and severity of COPD and increased severity of smoking status. Regarding the smoking status of COPD patients, there was a highly significant difference for the measured TNF-α (53. 74 ± 9.52 versus 12.73 ± 1.20 with $p < 0.0001$) with no significant difference for the measured hs-CRP (3.87 ± 0.29 versus 3.58 ± 0.27 with $p > 0.05$). Interestingly, there were significant negative correlations between the levels of TNF-α and hs-CRP, and FEV1 in stages II, III, and IV of COPD.

Conclusions: The circulating levels of the inflammatory markers hs-CRP and TNF-alpha are significantly elevated in patients with stable COPD and these biomarkers could be used as predictor factors for severity of inflammation in COPD patients. Longitudinal studies evaluating the effects of smoking cessation on bronchial and systemic inflammation are needed to allow better understanding of these relationships and their consequences.

Introduction

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized and defined by a single physiological parameter: limitation of expiratory air-flow which, most often, is slowly progressive over the years. According to the widely accepted definition from Global Initiative on Obstructive Lung Disease (GOLD) COPD is "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases" [44]. COPD is a condition characterized by an abnormal inflammatory response beyond the lungs with evidence of low-grade systemic inflammation which causes systemic manifestations such as weight loss, skeletal muscle dysfunction, an increased risk of cardiovascular disease, osteoporosis and depression, among others [6,45]. Several studies have shown systemic inflammation in COPD patients with increased neutrophil, macrophage, and T-lymphocyte numbers and high concentrations of inflammatory mediators in peripheral blood (C-reactive protein (CRP) and TNF-α) [11,1]. Airway inflammatory markers are higher in more severe disease and increase during COPD exacerbations. However, no exhaled biomarker has been widely used in clinical trials in COPD [7]. Kostikas et al. [12] stated that systemic inflammation is present in stable COPD and the intensity of the inflammatory process relates to the severity of the underlying disease. In the interest of improving the diagnosis of COPD, several types of biomarker have been measured that are related to disease pathophysiology and the inflammatory and destructive process in the lung. However, there is little information about biomarker reproducibility and the relationship with disease development, severity, or progression [9]. Several inflammatory markers such as C-reactive protein (CRP), fibrinogen and IL-6, are increased in patients with COPD in both stable disease and exacerbations, with CRP being the most studied biomarker [5]. One of the inflammatory markers which is increasingly evaluated in COPD patients is CRP. CRP is an acute phase protein synthesized predominantly by the hepatocytes in response to tissue damage or inflammation. It has been accepted that levels of CRP relate to the presence of airflow obstruction [44]. Very little is known about the mechanism of increased TNF-α concentration in the plasma of COPD patients and its relationship with disease severity and active smoking has not been established [9,15]. Tobacco smoking is the main risk factor of chronic obstructive pulmonary disease (COPD) but not all smokers develop the disease. An abnormal pulmonary and systemic inflammatory response to smoking is thought to play a major pathogenic role in COPD, but this has never been tested directly. Yet, only a proportion of smokers, so called "susceptible smokers", develop the disease [42,3]. The genetic and epigenetic background of each smoker is likely to regulate the type and intensity of his/her inflammatory response to smoking [10]. In "susceptible smokers", this response is thought to be "enhanced", both in the lungs and in the systemic circulation, and is believed to drive disease progression [41]. However, despite the wide acceptance of this notion, no previous study has actually studied the "response" to smoking (i.e., the specific inflammatory changes that occur before and after smoking) in susceptible smokers (i.e., patients with COPD) and resistant smokers (i.e., smokers with normal spirometry) [3]. Long-term smoking causes airway inflammation characterized by neutrophil, macrophage, and activated T lymphocyte infiltration and by increased cytokine concentrations such as tumor necrosis factor-alpha (TNF-α), interleukins (IL)-6 and IL-8 [4,2,14]. Although nearly all smokers show some evidence of lung and systemic cellular and/or humoral inflammation, only a few will suffer an amplified response and develop COPD. The aim of this study was to identify whether the inflammatory process in stable COPD patients is powerful enough to produce significant changes in the selected inflammatory markers (TNF-α and hs CRP). The role and levels of TNF-α and hs CRP in the peripheral circulation of COPD patients and the relationship between these biomarkers with prognostic factors in COPD will be investigated and as we hypothesized that smoking exposure will induce a different inflammatory signature, the impact of smoking on inflammatory biomarkers in patients with chronic obstructive pulmonary disease will be evaluated. With the development of many new drugs that target inflammation in COPD, there is a pressing need to identify reliable biomarkers that may indicate whether an anti inflammatory therapy is likely to have clinical benefit. A major problem is the lack of any gold standard anti inflammatory therapy that is effective in COPD, as a yardstick to compare potential therapies.