Outcome of Smoking Cessation on Airway Remodeling and Pulmonary Inflammation in COPD Patients

Esmaeil Mortaz [1,2], Mohammad Reza Masjedi [2] and Irfan Rahman [3]

[1] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands [2] Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, and [3] Lung Biology and Diseases Program, Department of Environmental Medicine and Pulmonary Medicine, University of Rochester Medical Center, Rochester, USA.

INTRODUCTION

There are currently more than 1.3 billion tobacco smokers in the world according to the World Health Organization (WHO) (1). It has been demonstrated that cigarette smoking is the most important risk factor for the development and progression of chronic obstructive pulmonary disease (COPD), and accounts for about 80% of COPD cases (2, 3). COPD, a term referring to two respiratory system diseases: chronic bronchitis and emphysema, is characterized by an airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and related to the abnormal inflammatory response of the lungs to inhaled noxious particles or gases (4, 5).

It has been reported that 10% to 15% of all smokers (6) and up to 26% of heavy smokers develop COPD (7). As the prevalence of smoking has risen among females and decreased slightly among males, the sexual distribution of COPD

Correspondence to: Irfan Rahman
Address: Department of Environmental Medicine and Pulmonary Medicine, University of Rochester Medical Center, Rochester, USA
Email address: irfan_rahman@urmc.rochester.edu

deaths has shifted from 19% female in 1970 to 38.5% in 1993 (8).

Cigarette smoking, especially heavy smoking, long duration of smoking, and smoking of high-tar cigarettes accounts for important factors that contribute to the progression of COPD (9). Cigarette smoke contains more than 4000 deleterious chemical compounds, of which 200 are very toxic, and 10^{17} free radicals/oxidants per puff (10). In general, it has been accepted that the treatments available for COPD reduce the number and severity of exacerbations and restablish symptoms. However, available treatment do not aide in tackling the cause and ongoing problems of the disease, and have a limited effect on slowing down the progression of lung damage and inflammation (11).

Smoking cessation is considered as the first treatment in patients with chronic COPD. Its effect on airway inflammation in COPD is not well described, although cross-sectional studies suggest ongoing inflammation in ex-smokers (12). So far, smoking cessation is considered the only effective

treatment for avoiding or reducing the progression of COPD (13). There are several smoking cessation medications and devices available commercially. However, there are contradictory observations regarding the effect of smoking cessation on airway inflammation and remodeling associated with COPD including the use of smoking cessation medications and devices. Studies in COPD patients indicated that smoking cessation improves respiratory symptoms, reduces loss of pulmonary function and decreases lung inflammation and oxidative stress (14-19), whilst some studies indicated that smoking cessation fails to reverse the chronic airway inflammation (19-21). Unfortunately, there is insufficient observation available regarding the effects of smoking cessation on pro-inflammatory mediators levels, which do play a pivotal role in the pathogenesis of COPD. In the following sections, recent studies on the potential role of cigarette smoke cessation on the progression and development of COPD is summarized.

Evidence of animal modeling of lung emphysema

As indicated earlier, there is contradictory data available on the role of quitting cigarette smoking as it relates to the development of lungs injury and inflammation. This is due to the insufficient evidence on the effects of smoking cessation and the release of inflammatory mediators, which do play an important role in airway inflammation and tissue remodeling seen in COPD. Therefore, an animal model of cigarette smoke-induced lung emphysema usually is practical.

In this regard, the severity of airway remodeling and inflammation was assessed by analyzing the alveolar enlargement, heart hypertrophy, and inflammatory cells in the BALF and lung tissue and by determining the profiles of cytokine and chemokine in the BALF of animals.

Wright et al. (22) and March et al. (23), for the first time demonstrated that emphysema was still present in guinea pigs and mice after smoke exposure followed by a smoking cessation period. Thereafter, Vernooy et al (24) found that the long-term LPS exposure results in irreversible alveolar enlargement in mice.

Recently Braber et al described the alveolar enlargement and right ventricle heart hypertrophy in smoke-exposed mice remained unchanged, however the neutrophilic inflammation of BALF was decreased, and levels of IL-12 in BALF remained at high levels after smoking cessation. It has been shown that cigarette smoke-enhanced VEGF levels did not significantly change after smoking cessation (25). In conclusion, animal models of CS-induced lung emphysema could partially regressed after smoke-cessation/stopping the CS exposures.

Clinical observations

Now it is clear that the treatment of COPD should begin at an early stage of the disease and smoking cessation is an important therapeutic mode in patients with COPD. Exposure to cigarette smoke activates the inflammatory cascade in the airways, resulting in the production of a number of potent cytokines and chemokines with accompanying damage to the lung epithelium, increased permeability, and recruitment of inflammatory cells into the lungs (26, 27).

It is known that CS- and other environmental exposure-induced progressive lung injury and inflammation play a crucial role in pathogenesis of COPD. In this scenario, excessive shedding of columnar cells may be the initial response, followed by the mobilization of neutrophils and then macrophages (26). Both of these inflammatory cells, by releasing the proteases enzymes may be involved

in the breakdown of the supporting connective tissue of the lung. The lung macrophages begin to clean up the foreign matter, becoming pigmented (28) later, mucous gland hypertrophy and excessive production of mucus develops, resulting in mucous casts, which can plug the small airways. This may be followed by transformation of the columnar mucosa to a self-protective metaplastic and then a potentially premalignant dysplastic surface.

It has been shown that quitting smoking induces a generally opposite effects. The numbers of neutrophils and of macrophages dropped significantly in the first few samples after quitting smoking. Columnar cell counts seemed to fall after a four- to six-months delay, but statistically when averaged over a twelve month period, there were no significant changes seen in those who stopped smoking compared with those who did not. The quantity of mucus in the specimens did not fall significantly, although in non-quitters there was a significant increase over the baseline levels. Whereas macrophages (non-pigmented and pigmented), neutrophils, mucus, and columnar cells are present to some degree in all sputa, mucous spirals are not. For the individual who successfully stopped smoking, there may be few if any signs of recovery in lung function during the critical six months to one year when most recidivism occurs (13).

The effects of long-term smoking cessation over a five year period, studied by Scanlon et al., described that participants who stopped smoking experienced an improvement in FEV1 in the year after quitting (an average of 47 ml or 2%) (15). To gain insight into the underlying pathophysiological mechanisms of cigarette smoke cessation, many laboratories investigated the airway inflammation in bronchial biopsies and sputum samples (29). In one study of symptomatic COPD patients, who successfully quit smoking showed airway inflammation persisted in bronchial biopsies, while the number of sputum neutrophils, lymphocytes, interleukin (IL)-8, and eosinophilic-cationic-protein levels significantly increased at 12 months. In the same study of asymptomatic smokers who successfully quit, inflammation significantly reduced (i.e. the sputum macrophages, percentage of eosinophils and CXCL-8 levels) or did not change (29). Interestingly, Turato et al have described that the inflammatory process present in the airway mucosa of current smokers may persist after smoking cessation in subjects who continue to have symptoms of chronic bronchitis (21).

Conclusions, further questions and outlook

As indicated earlier, smoking leads to irreversible lung emphysema and heart hypertrophy. The inflammatory process in the airways and lungs of COPD patients caused by cigarette smoke exposure were only partially reversed after smoking cessation. There still needs to be an increase in the awareness of smoking cessation for patients with other disorders such as cardiovascular diseases, however, the following factors should be of focus for tobacco control in the following groups/classes of patients: younger in age, low socio-economic status, patients with smoking family members, patients with a higher body mass index, and higher total family income.

In conclusion, it is now clear that smoking cessation should be considered as a first step to halt in the decline and progression of lung emphysema, inflammation, and oxidative stress. An additional medication and support could be provided to tackle chronic respiratory symptoms involving inflammation (See table 1).

Table 1. Effects of smoking cessation on inflammation cells and lungs function.

Studies	Inflammation	Disease condition
Skold et al (13)	Decreased amount cells in BALF	No effects on FEV1
Swan et al. (14)	Decreased macrophages, neutrophils	Reduction in pulmonary functions
Scanlon et al.(15)	Decreased macrophages, neutrophils	Improvement of lung function in FEV1
Pelkonen et al. (16)	Not reported	Reduced decline of FEV1
Godtfredsen et al. (12)	Not reported	?
Willemse et al. (20)	Increased inflammatory cells in BALF	Improved the decline of lung function
Turato et al. (21)	Increased number of macrophages in bronchial airways	Not reported
Wright et al. (22)	lung emphysema is progressive	Not reported

Abbreviations:
BALF; Bronchoalveolar lavage fluid; COPD; Chronic Obstructive Pulmonary Disease; CS; Cigarette smoke; ROS; Reactive oxygen species; FEV1; Forced Expiratory Volume

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