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ORIGINAL ARTICLE

Evaluation of matrix metalloproteinase-9 and tissue inhibitor metalloproteinase-1 levels in bronchoalveolar lavage of apparently healthy smokers

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KEYWORDS

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Abstract Cigarette smoking has a destructive effect on the extracellular matrix (ECM), so it is considered the most important risk factor for the development of emphysema as it leads to recruitment of activated macrophages and neutrophils in the lung leading to release of proteolytic enzymes as matrix metalloproteinases (MMPs) or an imbalance between MMPs and the tissue inhibitors of MMP (TIMPs), playing a role in the pathogenesis of emphysema.

Aim of the work: The aim of this work was to evaluate the level of MMP-9 and tissue TIMP-1 in bronchoalveolar lavage of apparently healthy smokers.

Methods and results: MMP-9 and TIMP-1 levels were measured by ELISA in BAL in 10 healthy controls, 15 apparently healthy smokers and 15 emphysematous patients. Smokers and COPD patients had a higher concentration of MMP-9 and TIMP-1 compared with controls. The ratio of MMP-9 to TIMP-1 was significantly higher in the emphysema group than the two other groups. Also the smoker group was higher than the control group but without statistic significant difference.

Conclusions: Healthy smokers had a higher concentration of total MMP-9 and that concentration was correlated with their exposure to tobacco smoke. Maintenance of normal MMP-9/TIMP-1 ratio in healthy smokers may explain the absence of progressive airway obstruction. Measurement of active MMP-9 concentration could be useful for assessment of airway remodeling.

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Introduction

Airway inflammation of emphysematous patients appears to be an amplification of the normal inflammatory response of

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respiratory tract to chronic irritants such as cigarette smoke which is the major risk factor for emphysema. This amplification is attributed to two mechanisms oxidative stress and excess of proteinases in the lung [1].

The extracellular matrix (ECM) is a dynamic structure and equilibrium between synthesis and degradation of ECM is required for maintenance of its homeostasis [2].

Matrix metalloproteinases (MMPs) can degrade any of matrix constituents such as collagen, elastin, basement membrane, laminin, and fibronectin. The balance between MMPs and their inhibitors is critical in tissue repair and remodeling and its disturbance plays an important role in the pathogenesis of emphysema [3].

One of macrophage-derived MMPs is MMP-9 which is capable of degrading type IV collagen. It is present in low quantities in healthy lung, but much more abundant in several lung diseases, including COPD, asthma and IPF [4].

Macrophage also produces tissue inhibitors of metalloproteinases (TIMPs), which bind to the active forms of MMPs. In addition, TIMP-1 binds to pro-MMP-9 [5].

Several studies suggest that the balance between regulated macrophage MMP-9 and TIMP-1 plays a key role in cigarette smoke induced emphysema, which may be an important determinant of clinical expression of COPD as emphysematous patients show increased expression of MMP-9 [6]. The two main elastase producing cell types in the airways of smokers are neutrophils and macrophages, but macrophages are by far the most abundant cell type in the bronchoalveolar spaces in cigarette smokers. This may suggest a positive correlation between MMP-9 activity and the degree of air flow limitation. This makes smokers have a higher prevalence of respiratory symptoms, lung function abnormalities, and greater COPD mortality rates than nonsmokers [7].

Emphysema is characterized by specific inflammatory cells involving neutrophils, macrophages and lymphocytes. These cells release inflammatory mediators (chemotactic factors) that can attract more inflammatory cells, amplify the inflammatory process [8].

Aim of the work

The aim of this work was to evaluate the levels of MMP-9 and TIMP-1 in the BAL in apparently smokers in comparison to emphysematous patients.

Subjects and methods

This work was carried out in the Chest Department, Tanta University Hospital on 40 male subjects; during the period from February 2012 to June 2013. They were classified into 3 groups.

Group I: Included 10 apparently healthy non smoker volunteers, their ages ranged from 45 to 55 years (control group).
Group II: Included 15 apparently healthy smoker volunteers, their ages ranged from 44 to 59 years, with smoking index ranging from 7 to 20 pack/year (smoker group).
Group III: Included 15 of emphysematous patients and their ages ranged from 48 to 65 years. Their smoking index ranged from 13 to 22 pack/year. (COPD group).

Written consent was obtained from all participants in this research.

Inclusion criteria of mild–moderate emphysema

Severity was assessed according to Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD 2011).

Patients group A: Low risk, less symptoms. Typically GOLD 1 or GOLD 2 (Mild: FEV1/FVC ratio $< 70\%$, and FEV1 $\geqslant 80\%$ predicted, or Moderate: FEV1/FVC ratio $< 70\%$, and $50\% \leqslant$ FEV1 $< 80\%$ predicted) and/or 0–1 exacerbation per year and mMRC grade 0–1.

Patient group B: Low risk, more symptoms. Typically GOLD 1 or GOLD 2 and/or 0–1 exacerbation per year and mMRC grade $\geqslant 2$.

Exclusion criteria

Patients with upper or lower respiratory tract infection during the last 2 months preceding the study or associated bronchiectasis, bronchial asthma, lung cancer, known α1-antitrypsin deficiency, acute exacerbation in the 4 weeks preceding the study and patients with respiratory failure, heart failure or any other organ failure.

Methods

The following were done for all subjects.

Thorough history taking, complete general and local examination, chest X-ray, CBC, CT scan for emphysematous patients to detect mild emphysematous changes in early cases and exclude any other pathology, pulmonary function tests including FVC, FEV1, and FEV1/FVC before and after inhalation of B_2 agonist. Bronchoalveolar lavage (BAL) was done via fiberoptic bronchoscope for all groups, the collected BAL was centrifuged for 10 minutes measured for BAL total and differential cell count. The supernatant was stored at -80 °C until later examination for estimation of gelatinase B (MMP-9) and (TIMP-1) by ELISA technique.

Results

The mean value and SD of FEV1, FVC, and FEV1% were significantly lower in the COPD group than the smoker and

Table 1 Comparison of mean value of some spirometric data between studied groups.

Variables	Group I	Group II	Group III	*F*	*p*
FEV1% of predicted					
Range	95–98%	87.5–94%	60–84%	20.362	0.001*
Mean	96.35	90.13	73.2		
SD	±1.22	±2.21	±7.77		
FVC% of predicted					
Range	97–110%	70–100%	63–95%	8.133	0.001*
Mean	98.1	94.16	79.06		
SD	±7.70	±22.47	±4.96		
FEV1/FVC% of actual					
Range	80–89%	79–85%	50–70%	16.388	0.001*
Mean	82.6	81.3	69.1		
SD	±2.7	±2.3	±3.5		

* Significant *p* value < 0.05.