Expression of Adhesion Molecules in Non-smokers, Smokers and Patients With Chronic Obstructive Pulmonary Disease

Şükran Atikçan, MD[1]; Ahmet Selim Yurdakul, MD[1]; Filiz Çimen, MD[1]; Nevin Taci, MD[1]; Mustafa Balcı, MD[2]

[1]Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Chest Diseases and Tuberculosis, Ankara, Turkey
[2]Türkiye Yüksek İhtisas Education and Research Hospital, Biochemistry, Ankara, Turkey

Abstract

The initial stage of inflammation of COPD is induced by releasing of leukocyte endothelial adhesion molecules. The aim of this study is to investigate the levels of LFA-1, Mac-1, and sICAM-1 in stable patients with COPD, healthy smokers and non-smokers, and to determine the role of adhesion molecules in the development of COPD.

We investigated Mac-1, LFA-1 and sICAM-1, which are adhesion molecules in the peripheral blood samples of stable patients with COPD (n= 50), healthy smokers (n= 25), and healthy non-smokers (n= 15). Furthermore, patients with COPD were divided into two groups as smoking COPD patients (n= 35), and biomass COPD patients (n= 15).

The level of sICAM-1 was measured quantitatively with ELISA method. Flow cytometry was used for Mac-1 and LFA-1 levels.

No statistically significant difference was found in LFA-1 and sICAM-1 levels among the groups ($p>0.05$). But Mac-1 levels were higher in the healthy smokers when compared to stable patients with COPD (97.8±2.5 vs 92.3±5.9, $p<0.05$) and no statistically significant difference was found between non-smokers and smokers ($p>0.05$). In addition, while there was statistically significant difference between smoking COPD patients and healthy smokers in terms of Mac-1 levels (93.7±6.6 vs 97.8±2.5, $p<0.05$), no difference was found between biomass COPD patients and other groups ($p>0.05$). There was a negative correlation between FEV_1 and both Mac-1 level ($r=-0.302$, $p=0.037$), and sICAM-1 ($r=-0.346$, $p<0.001$). In addition, there was a negative correlation between LFA-1 level and $PaCO_2$ ($r=-0.387$, $p=0.007$).

As a result, we found that there was an increase in adhesion molecules through inducing of inflammation and other stimulants because of smoking. However, we also determined that there were no important changes in releasing of adhesion molecules in stable patients with COPD.

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Introduction

The activation of inflammatory cells like neutrophils, macrophages, and lymphocytes is very important in the pathogenesis of COPD (1). It is known that the initial stage of inflammation of COPD is induced by releasing of leukocyte endothelial adhesion molecules on endothelial cell surfaces. Adhesion molecules, which act as ligands for leukocyte cell receptors, moderate the adhesion of leukocytes to the endothelium before being extravasation into tissue (2-4).

The inflammation in parenchyma and peripheral airways of the patients with COPD has been proved with tissue biopsies. Oxi-

Corresponding Author: *Dr. Ahmet Selim Yurdakul*
Phone : +90 (312) 364 81 87
E-mail : ahmetselimyurdakul@hotmail.com

dative stress has an important role in the accumulation of inflammatory cells, and an indication of this event is the adhesion molecules released from leukocytes (5,6).

Inflammatory process has recently been shown to be regulated by a group of molecules that are termed adhesion molecules and consist of three subfamilies: selectins, the immunoglobulin supergene family, and integrins (7). Membrane attack complex (Mac-1) is one of the integrin molecules, and it locates on the surface of the leukocytes as a result of cell activation, and responds to the movement and chemotaxis of the leukocytes in the vascular bed. Soluble intercellular adhesion molecule-1 (sICAM-1) is an inducible surface glycoprotein, and is capable of binding lymphocyte function-associated antigen-1 (LFA-1) and Mac-1. sICAM-1 is released in low levels on endothelial cell membranes, and is stimulated markedly when encounters inflammatory cytokins. LFA-1 is a smaller molecule than sICAM-1, and is released from endothelial cells (8,9). It is reported that releasing of adhesion molecules increases in conditions with inflammations like asthma, allergic rhinitis, COPD, bronchiectasis, cystic fibrosis, diffuse pan-bronchiolitis, and adenoviral respiratory infections (10-17).

We aimed to investigate the levels of LFA-1, Mac-1, and sICAM-1, which are adhesion molecules, in stable patients with COPD, healthy smokers and healthy non-smokers as a control group, and to evaluate the relationship between the inflammation develops as a result of smoking and the inflammation seen in the pathogenesis of COPD, and to determine the role of adhesion molecules in the development of COPD.

Material and Methods

Population and Ethics

Fifty stable patients with COPD, 25 healthy smokers, and 15 healthy non-smokers as a control group were enrolled in this study (Table 1). Patients with COPD were defined as a postbronchodilator FEV_1<80% of the predicted value in combination with an FEV_1/FVC <70% and have no exacerbations, defined as increased dyspnea associated with a change in quality and quantity of sputum that had led the subject to seek medical attention, nor had they received glucocorticoids or antibiotics within the preceding month (18). Healthy smokers and non-smokers had a baseline FEV_1 greater than 85% of the predicted value. In addition, COPD patients were divided into two sub-groups as the smoking COPD patients, and biomass COPD patients.

Table 1. The demographic characteristics of the study population

	Sex F/M	Age (years)	Cigarette (pack-year)	FEV_1 (%)
COPD Patients (n=50)	13/37	59.5±10.7	35.9±34.6	61.6±13.3
Smoking COPD patients (n=35)	2/33	59.6±11.1	51.3±30.2	63.2±12.9
Biomass COPD patients (n=15)	13/2	59.3±10.1	-	57.8±13.6
Healthy smokers (n=25)	11/14	43.8±7.3	26.9±13.3	92.3±19.7
Non-smokers (n=15)	7/8	48.5±6.6	-	94.6±11.7

The smoking history of the stable COPD patients and healthy smokers was 35.9±34.6, 26.9±13.3 pack-year, respectively. Pack-year were expressed as the numbers of packs per day x the duration of smoking (years). All of the healthy smokers were current smokers but all of the smoking COPD patients were ex-smokers.

The criteria for exclusion from the study were as follows: clinically unstable patients with COPD, individuals with coexistent disorders like bronchial asthma, bronchiectasis, lung cancer, individuals with any immunosuppresive disorder or individuals who have used drugs with such effects in their personal history, patients with COPD using oral or inhale steroids, individuals who smoke less than 5 pack-year, individuals with abnormal pulmonary function tests in smokers and the control group, individuals with any infectious respiratory disease or individuals using drugs, pregnant or lactating women, individuals under eighteen years old, and individuals who failed in giving informed written consent.

All of the patients gave their written informed consent, having been informed about the details of the study. This study was conducted in accordance with the Declaration of Helsinki amended the 52nd WMA General Assembly (Edinburgh, 2000), and approved by local ethics committees.

Methods

We collected the blood samples from all our subjects in the morning. All current smokers had not smoked for 8 hr before the blood sample. Measurement of adhesion molecule levels from peripheral venous blood samples of all the individuals taken in this study was carried out in double-blind fashion.

Determination of sICAM-1, Mac-1 (CD11b7CD18), LFA-1

Commerical ELISA kit (Bender MedSystem, Vienna, Austria) was used for quantitative detection of sICAM-1 in serum samples. Removed the serum from the clot or red cells, respectively as soon as possible after clotting and seperation. Samples were stored –20°C to avoid loss of bioactive sICAM-1. Test principle in brief, an anti sICAM-1 monoclonal coating antibodies adsorb to the microwells; a HRP conjugated monoclonal anti-sICAM-1 antibody was added and to sICAM-1 captured by first antibody. Following incubation unbound enzyme conjugated anti-sICAM-1 was removed during a wash step and substrat solutions reactive with HRP

were added to the wells. A coloured product was performed in proportion to the amount of sICAM-1 present in the samples. The reaction was terminated by addition of acid and absorbance was measured at 450 nm. A standart curve was prepared from five sICAM-1 standart dilutions and sICAM-1 sample concentrations (ng/ml) were determinated. Mac-1 (CD11b7CD18) and LFA-1 adhesion molecule expressions were measured by dying of periferal blood neutrophils with direct single stain immune fluorescence technique. Flow cytometry was performed with a FACScan (Becton Dickinson, Heidelberg, Germany). Murine originated antihuman monoclonal antibodies conjugated with fluorescein isothiocyanated (FITC) and phycoerythrin has used. Monoclonal antibodies were provided from Becton Dickinson. In brief, 100 mL blood sample was mixed 20 mL monoclonal antibodies. After incubation at 4°C for 20 min damage erythrocytes were washed out. Remaining leukocytes were fixed with formaldehyde. Cellquest (Becton Dickinson) software was used for flow cytometric analysis. The mean fluorescence intensity within a gate was taken as a measure of antibody binding. Results are given in the percentage increase or decrease of the measure compared with the values determinated at the measures of the blood samples taken control groups. We compared the percentages obtained from the healthy control group with the percentages of the patient group (COPD patients, smokers group). We evaluated whether the differences between these two percentages were statistically significant or not. In addition, arterial blood gas analyses were performed in all subjects.

Statistical Analysis

Data processing and statistical analysis were performed using GraphPad InStat (V2.04a). One-way ANOVA test was used for the comparison of the distribition of the levels of LFA-1 among the groups. Kruskal-Wallis test was used to compare the differences among the groups for the sICAM-1 and Mac-1 levels. Mann-Whitney U-test by using Bonferroni correction were performed in order to analyse if there were significant differences between groups. Spearman's correlation test and Pearson's correlation test were used to examine associations between the levels of sICAM-1, LFA-1, Mac-1, and FEV_1, pH, PaO_2, $PaCO_2$, O_2sat, age, sex. All data were expressed as means ± standard deviation expect LFA-1 and sICAM-1 levels. Data are presented as median range (min-max) for the LFA-1 and sICAM-1 levels. P value of less than 0.05 was accepted as statistically significant.

Results

In this study, no statistically significant differences were found among COPD patients, healthy smokers and non-smokers in terms of LFA-1 and sICAM-1 levels ($p>0.05$). However, it was found that there was a statistically significant difference between COPD patients and healthy smokers in Mac-1 levels ($p<0.05$, Table 2).

Table 2. The level of LFA-1, sICAM-1 and Mac-1 in the study subjects

	LFA-1sI	CAM-1	Mac-1
COPD Patients (n=50)	35.5(1-70)	408.5(94-861)	92.3±5.9
Smoking COPD patients (n=35)	35.5(1-70)	420(240-861)	93.7±6.6
Biomass COPD patients (n=15)	36(2-66)	372(94-621)	95.5±3.9
Healthy smokers (n=25)	33(3-78)	407.5(178-611)	97.8±2.5**
Non-smokers (n=15)	39(8-68)	364(164-587)	97.1±3.4

Data are presented as mean±SD for Mac-1 and are presented as median range (min-max) for LFA-1 and sICAM-1. **Represents significant difference compared with COPD patients and smoking COPD patients ($p<0.05$).

There were no statistically significant differences among smoking COPD patients, biomass COPD patients, healthy smokers and non-smokers in terms of levels of LFA-1 and sICAM-1 ($p>0.05$). However, there was a statistically significant difference between smoking COPD patients and healthy smokers groups in Mac-1 levels ($p<0.05$, Table 2).
In addition, there was a negative correlation between FEV_1 and both Mac-1 level ($r=-0.302$, $p=0.037$) and sICAM-1 ($r=-0.346$, $p<0.001$, Table 3). The negative correlation between FEV_1 values and Mac-1 levels is a relationship unique for COPD patients. While no correlation was found between pH, PaO_2, O_2 sat and LFA-1 level, there was a negative correlation between the levels of $PaCO_2$ and LFA-1 ($r=-0.387$, $p=0.007$, Table 3). No correlation was found between Mac-1 and sICAM-1 levels and pH, $PaCO_2$, PaO_2, O_2 sat ($p>0.05$).

Table 3. The correlations between adhesion molecules and FEV_1, arterial blood gas and age

	FEV_1	pH	PaO_2	$PaCO_2$	O_2sat	Age
sICAM-1	r=-0.346, p<0.001	r=0.101, p>0.494	r=-0.248, p>0.090	r=0.062, p>0.674	r=-0.237, p>0.105	r=0.262, p>0.072
LFA-1	r=0.105, p>0.478	r=0.218, p>0.137	r=0.243, p>0.096	r=-0.387, p=0.007	r=0.216, p>0.139	r=0.202, p>0.168
Mac-1	r=-0.302, p=0.037	r=-0.099, p>0.502	r=-0.041, p>0.782	r=-0.132, p>0.372	r=-0.110, p>0.455	r=0.079, p>0.595

Discussion

COPD is thought to be not limited to pulmonary inflammation and structural remodeling, and to modify functions of

other organs and biochemical parameters (19). In addition, systemic oxidative stress occurs in peripheral blood of patients with COPD during exacerbations and up-regulates the expression of the adhesion molecules (20,21). Adhesion molecules serve as ligands for leukocyte cell receptors, mediating the adhesion of leukocytes to the endothelium prior to their subsequent extravasations into inflamed tissue (22). We could find no statistically significant difference when we compared stable patients with COPD and non-smokers in terms of sICAM-1, LFA-1, and Mac-1 adhesion molecules. But, Mac-1 levels were higher in the healthy smokers when compared to stable patients with COPD and there was a negative correlation between FEV_1 and both Mac-1 level and sICAM-1. In addition, there was a negative correlation between LFA-1 level and $PaCO_2$.

sICAM-1 is an adhesion molecule with endothelial origin. Releasing of sICAM-1 is normal as long as the integrity of the endothelium is maintained. sICAM-1 levels increase when the permeability of endothelium is ruined and cause inflammation and decrease when there is endothelial damage. Noguera et al. demonstrated that neutrophil Mac-1 expression was up-regulated in association with down-regulation of sICAM-1 in COPD patients (23). These findings are theoretically correct. But, Riise et al. reported increased expression of sICAM-1 and E-selectin in serum of the COPD patients as compared to the controls (2). In addition, Di Stefano et al. found increased of ICAM-1 on the basal epithelial cells. They stated that the increased E-selectin and ICAM-1 expression in COPD reflects an ongoing inflammatory response to a persistent stimulus that may act independently of clinical exacerbations (13). These results support the hypothesis that high levels of circulating adhesion molecules may be associated with an upregulation of cell adhesion molecules on endothelial and epithelial surfaces in COPD. In our study, ICAM-1 was clearly but not significantly increased by comparison with normal subjects. Gonzales et al. showed a distribution of adhesion molecules that was consistent with the inflammatory response in the airways and parenchyma of heavy smokers but failed to show any differences between these with or without airways obstruction. They indicated that these adhesion molecules have no any particular role in the pathogenesis of the structural changes in the airways responsible for the obstruction that occurs in a proportion of the smoking population (24). And also, Noguera et al. observed reduced ICAM-1 levels in patients with COPD (23). This condition was explained with the endothelial damage and the reducing of ICAM-1 levels in patients with COPD. On the other hand, it was observed that endothelial function appears to be abnormal in smokers, but ICAM-1 levels did not decrease in the other studies (24,25).

In the studies performed on the measurements of adhesion molecules in chronic respiratory illness, results are rather diverse and controversial. In fact, we believe that more detailed and meticulous studies must be carried out with greater number patients and patient groups.

While smoking is the major factor in the development of COPD, exposure to biomass also causes the development of COPD. Especially in women, the greatest cause of COPD development is exposure to biomass (26). The inflammatory mechanism in the tissues of the lung parenchyma is triggered through exposure to biomass. Consequently, similarities can be expected in the results of the adhesion molecules since the reactions of the tissues to the chemical irritants related to smoking and exposure to biomass are the same. No study was found on the measurements of adhesion molecules in a group consisting of patients with COPD as a result of exposure to biomass.

Mac-1 is a molecule, classified as one of the leukocyte integrins that settles at leukocyte surface after the activation of the cell. This molecule is responsible for the chemotaxis and movement of the leukocyte in the vascular bed (27). We found that the Mac-1 levels of healthy smokers were significantly higher than that of stable COPD patients. Following smoking, epithelial integrity is broken especially in peripheral airways, and as a response to releasing of free oxygen radicals and various chemicals found in cigarettes, neutrophil migration to the area occurs. The increased neutrophil migration induces the inflammation and releasing of adhesion molecules also increases. This situation is an indication of the increased oxidative stress in peripheral airways (21,28,29). Mac-1 is important in the activation of the respiratory burst (30). Neutrophils sequestered in the pulmonary circulation following cigarette smoke inhalation in the rabbit show increased expression of CD18 integrins (31). Furthermore, increase in neutrophil retention is observed in smokers, and in exacerbations in patients with COPD (32,33). Higher levels of Mac-1 levels in healthy smokers than that of patients with COPD may be explained with the clinical stability of COPD patients, continuous stimulant role of smoking in releasing of free oxygen radicals and in continuous neutrophil activation and causing faults in neutrophil functions. Takeuchi et al. studied effects of smoking cessation on soluble adhesion molecules by comparing ex-smokers with never-smokers. Levels of sICAM-1 and sE-selectin in ex-smokers remained significantly high compared with never smokers. They thought that smoking cessation did not restore the levels of any of the adhesion molecules in previously chronic smokers (25). Smoking leads to the activation of protein kinaz C, and binding of NF-kappa-B to the specific location of DNA, and consequently to the increased secretion of the adhesion molecules (34). Recent studies have shown that constitutively expressed Mac-1 in neutrophils is sufficient for the adhesion induced by single chemical stimulus while newly expressed Mac-1 participates in adhesion if neutrophils experience an increase in chemo-attractant stimuli (35,36).

We observed a negative correlation between sICAM-1 and Mac-1 levels, and FEV_1, but only for COPD patients, not all of the groups included in the study. In previous studies, it was shown that there was a negative correlation between sICAM-1 levels and FEV_1 in patients with asthma, COPD, and bronchiectasis according to the severity of the disease (13,14,37). sICAM-1 plays a key role in the dynamic regulation of the mechanisms of cell adhesion and migration responsible for cellular recruitment and activation in inflammation (38). As a result, adhesion molecules increase in secondary response to inflammation and oxidative stress. Smoking stimulates releasing of adhesion molecules by creating oxidative stress through neutrophil accumulation and dysfunction. The increase in adhesion molecules through the induction of inflammation by smoking indicates that smoking has an important role in the development and pathogenesis of COPD. But, there was no important change in releasing of adhesion molecules in stable COPD patients. Further studies of the function of adhesion molecules in COPD will contribute to our understanding of the pathogenesis of this disease and, through the development of specific antibodies, may provide new therapeutic approaches to the treatment of COPD.

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