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Pavlenko OB
(A) State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine", Department of Internal Medicine 1, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str
(B) MI "Dnipropetrovsk City Clinical Hospital #6" Dnipropetrovsk Regional Council, Dnepropetrovsk, str. Batumskaya 13

Correspondence
Pavlenko OB
(A) State Institution "Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine", Department of Internal Medicine 1, Ukraine, Dniepropetrovsk, 49000, 13, Batumskaya str
(B) MI "Dnipropetrovsk City Clinical Hospital #6" Dnipropetrovsk Regional Council, Dnepropetrovsk, str. Batumskaya 13

Condition of proteinase-inhibitory system in smoking patients with chronic obstructive pulmonary disease

Pavlenko OB

Abstract
Chronic obstructive pulmonary disease (COPD) is a problem whose urgency is growing rapidly around the world. The main risk factor for COPD development is smoking. Epidemiological studies, conducted in most countries of the world, found a significant increase in the number of patients among tobacco smokers. According to WHO, there are more than 1.1 billion of smokers all over the world, and it is the most common bad habit that leads to the occurrence of COPD.
Aim: To study the impact of smoking on the condition of proteinase-inhibitory system in patients with COPD.
Materials and methods: The study involved 164 men with COPD aged from 36 to 59 years, with disease duration from 9.2 to 15.3 years. Depending on the clinical and functional characteristics of the disease, the severity degree, as well as taking into account active smoking. To assess the nature and prevalence of chronic inflammation in COPD patients, fiber-optic bronchoscopy (FBS) was conducted.
To determine nicotine dependence in smokers, the questionnaire by K.O. Fagerstrom was used. Study of the activity of protease-inhibitory enzymes in bronchoalveolar fluid was conducted with conversion of enzyme activity in total amount of proteins by Lowry method.
Results: In bronchoalveolar fluid of patients with COPD, the imbalance in the protease-inhibitory system was revealed with predominance of proteinase potential: in smokers, the activity of TR group increases as compared with the group of healthy individuals and non-smokers with COPD. It has been found that the imbalance in protease-inhibitory system in patients progresses depending on the index "pack-years" of smoking. High rates of α2MH in bronchoalveolar fluid at increased inflammatory activity indicate that in the depletion α1AT, the present inhibitor can perform basic protection functions. It has been revealed that the most informative indicator in assessing the state of proteinase-inhibitory system in patients with COPD is the ratio of trypsin/α1antitrypsin.

Keywords: COPD, proteinase-inhibitory system, bronchoalveolar fluid, smokin

1. Introduction
Chronic obstructive pulmonary disease (COPD) is a problem whose urgency is growing rapidly around the world. Despite the advances in prevention and development of therapeutic intervention, COPD is the most common disease in the world and the leader by the frequency of complications.
According to WHO, this pathology occupies the 4th place among the leading causes of death. In Ukraine, the prevalence of COPD and bronchial asthma (BA) is very high, which affects the overall health of the nation as a whole and involves significant economic losses. In this regard, much research is devoted to further study of the issue [1].
The main risk factor for COPD development is smoking. Epidemiological studies, conducted in most countries of the world, found a significant increase in the number of patients among tobacco smokers. According to WHO, there are more than 1.1 billion of smokers all over the world, and it is the most common bad habit that leads to the occurrence of COPD.
According to the scientific literature, the development of lung disease in smokers results in the rapid formation of respiratory failure, emphysema and disability. Tobacco smoke is a trigger factor in the development of chronic inflammation in COPD, the manifestation degree of whose pathogenic effect depends on the inadequacy of protective systems of the body. One of the major systems of the body which control homeostasis is proteinase-inhibitory system, changes in which give rise to the development of diseases [3]. However, few research works have been devoted to study of the features of chronic lung disease in smokers; the prophylactic guidelines for this category of patients have not been developed.
In this regard, the study of the impact of smoking on the condition of biochemical processes in the lung tissue, particularly on the state of proteinase-inhibitory system, will further clarify the pathogenesis of COPD.

The aim of the research is to study the impact of smoking on the condition of proteinase-inhibitory system in patients with COPD.

2. Materials and methods of the research

The study involved 164 men with COPD aged from 36 to 59 years (average age – 52.1 ± 2.4 years) with disease duration from 9.2 to 15.3 years (on average – 11.5 ± 1.2 years). Depending on the clinical and functional characteristics of the disease, the severity degree, as well as taking into account active smoking, the following clinical groups were distinguished:

The 1st group included 84 patients with COPD [2]. Duration of smoking: from 20 to 35 years (on average 30.4 ± 1.8 years) and a high degree of nicotine dependence according to questionnaire by K.O. Fagerstrom.

Subgroup 1A − 28 patients with bronchial obstruction of 1 degree, clinical group A, acute stage, pulmonary insufficiency of 0 degree.

Subgroup 1B − 56 patients with bronchial obstruction of 3 degree, clinical group C, acute stage, pulmonary insufficiency of 2 degree.

The 2nd group included 80 patients with COPD who had never smoked.

Subgroup 2A − 32 patients with bronchial obstruction of 1 degree, clinical group A, acute stage, pulmonary insufficiency of 0 degree.

Subgroup 2B − 48 patients with bronchial obstruction of 3 degree, clinical group C, acute stage, pulmonary insufficiency of 2 degree.

The 3rd − control group, − included 32 men who had never smoked and as a result of clinical and laboratory studies have been diagnosed as apparently healthy.

To assess the nature and prevalence of chronic inflammation in COPD patients, fiber-optic bronchoscopy (FBS) was conducted.

To determine nicotine dependence in smokers, the questionnaire by K.O. Fagerstrom was used. Active habit of smoking was calculated in units of "pack-years". Patients with COPD of group 1 had a high degree of nicotine dependence according to the questionnaire by K.O. Fagerstrom, the total number of "pack-years" of smoking ranged from 5 to 30 (on average – 25.5 ± 1.2 "pack-years" of smoking).

The method to determine the activity of proteinase enzymes − trypsin, α1antitrypsin (α1AT), α2macroglobulin (α2MG) was based on the technique "Method for biochemical diagnostics of lung condition in bronchopulmonary diseases" [6].

Study of the activity of protease-inhibitory enzymes in bronchoalveolar fluid was conducted with conversion of enzyme activity in total amount of proteins by Lowry method [7].

Statistical analysis of the results was carried out on a personal computer using the "Microsoft Excel 97" software and the application package Statistica (license number 50083-005-4638086-02896) by conventional methods of variation statistics using Student's test and correlation analysis [4].

3. Results and Discussion

In bronchoalveolar fluid of patients with COPD, imbalance in the protease-inhibitor system was detected with predominance of proteinase potential. In the mild course of the disease in smokers, the level of TR activity increased by 3.2 times as compared with a group of healthy individuals, and by 1.6 times as compared with patients with COPD who do not smoke. With increased activity of trypsin (TR), the levels of protease inhibitors α1antitrypsin (α1AT) and α2macroglobulin (α2MG) significantly increase. Activity of α1AT in smokers increases by 1.7 times, α2MH – by 1.2 times as compared with the control group. In patients who do not smoke, the activity α1AT α2MH does not dramatically change. The most significant changes in the state of proteinase-inhibitory system were observed in the moderate course of COPD. In smokers, TR activity was increased by 4.5 times as compared with the group of healthy individuals and by 1.2 times as compared with non-smokers with COPD. In response to the increased activity of TR, the parameters of proteinase inhibitor activity significantly increased, activity α1AT increased by 1.9 times, α2MH − by 1.5 times as compared to control indicators ($p<0.05$) (see Table 1).

Analyzing the data, one can conclude that with the progression of the disease and increased severity degree, the activity of protease-inhibitory enzymes also increases and the imbalance between the protease potential and inhibitors activity appears.

Table 1: Parameters of activity of protease-inhibitory enzymes in bronchoalveolar fluid, depending on the severity of COPD

Subgroups of patients	1A	1B	2A	2B	3
Trypsin nmol/(c.l)	1.50±0.20*	2.10±0.10*■~	0.91±0.11*	1.72±0.20*	0.47±0.10
α1 anti-trypsin ncm/(c.l.)	1.44±0.10*	1.61±0.20*■~	0.88±0.09*	1.39±0.01*	0.84±0.02
α2 macroglobulin ncm/(c.l.)	0.015±0.001*	0.017±0.012*■	0.012±0.001*	0.014±0.001*	0.008±0.001

Notes:
1. *$p<0.05$ reliability of difference in the comparison with control indicators.
2. ~$p<0.05$ reliability of difference in the comparison of 1A-1B subgroups.
3. ■ $p<0.05$ reliability of difference in the comparison of 2A-2B subgroups.

In the study, we were interested in the previous diseases, which could provoke COPD. Important role in this regard belongs to acute bronchitis in the first place, and then chronic bronchitis, accompanied by cough syndrome, which is the background that gives rise to COPD in adulthood. Collecting the anamnesis, it has been revealed that in 69% of patients, previous cases of recurrent influenza were noted; 5% of cases suffered from tuberculosis in the childhood. Therefore, the onset of COPD against the background of frequent colds can be characterized as oligosymptomatic, undistinguished, but in adulthood it is manifested by progressive shortness of breath, changes in spirogram, and leads to the formation of irreversible changes in lung tissue.

The study found that the imbalance in the protease-inhibitory system in patients progresses according to the index of "pack-years" of smoking. High rates of α2MH in bronchoalveolar fluid at increased inflammatory activity indicate that in the depletion of α1AT, the present inhibitor can perform basic protection functions.

A direct highly probable correlation between the activity of TR and α1AT (r=0.72) has been found. Given the identified dependence, the ratio TR/α1AT was calculated. Based on the

analysis of clinical features of the disease, function parameters of external respiratory, values of activity of α1AT, TR and α2MH, as well as the TR/α1AT coefficient, it has been found that the value of TP/α1AT is of significant informational capacity and has a high probability regarding the course of the disease. The maximum values of TP/α1AT are registered in smokers with COPD of medium severe form; the minimum values were found in non-smokers with mild COPD.

In patients with an index up to 10 "pack-years" of smoking, the minimal changes in the activity of protease-inhibitory enzymes in bronchoalveolar fluid were revealed; the rate TR/α1AT in these patients ranged from 0.65 to 0.83. In patients with an index from 11 to 20 “pack-years” of smoking, a moderate imbalance in protease-inhibitory system was found; the ratio TR/α1AT in these patients ranged from 0.83 to 1.25. In patients with an index of "pack-years" 20 or above, the maximum protease activity of TR was detected against the background of a sharp decline in the activity of α1AT; these patients had the rate TR/α1AT of more than 1.25. Thus, the present study found that tobacco smokers, suffering from COPD, are characterized by the formation of higher levels of proteases, which leads to the imbalance in protease-inhibitory system and can lead to the destruction of lung tissue.

4. Conclusions

1. In bronchoalveolar fluid of patients with COPD, the imbalance in the protease-inhibitory system was revealed with predominance of proteinase potential: in smokers, the activity of TR group increases as compared with the group of healthy individuals and non-smokers with COPD.
2. It has been found that the imbalance in protease-inhibitory system in patients progresses depending on the index “pack-years” of smoking.
3. High rates of α2MH in bronchoalveolar fluid at increased inflammatory activity indicate that in the depletion α1AT, the present inhibitor can perform basic protection functions.
4. It has been revealed that the most informative indicator in assessing the state of proteinase-inhibitory system in patients with COPD is the ratio of trypsin/α1antitrypsin.

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