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EVALUATION OF OXIDATIV STATE PROTEINASE-INHIBITORY SYSTEM AND ENDOTOXICOSIS IN PATIENTS WITH COPD

Abstract. *The aim of the work was to study the relationship between indicators of proteinase-inhibitory system, oxidative stress and endotoxicosis in patients with COPD. 67 patients with COPD, men with an average age of 53.1±2.2 years, with the duration of the disease on average 12.5±1.7 years, in the stable phase of the pathological process with II-IV degrees of ventilation disorders according to the GOLD were examined. The activation of trypsin as an indicator of the state of the proteinase-inhibitory system involved in bronchopulmonary diseases pathogenesis, a probable decrease in the activity of its obligate α1-antitrypsin inhibitor, lipid peroxidation secondary metabolites accumulation, total antioxidant activity, molecules of average weight level increase in serum of COPD patients were found. At the examined patients endotoxicosis with initiation of disturbances of mechanisms of recovery in bronchopulmonary system is noted. Together, these events lead to a vicious circle of persistent inflammation, accompanied by chronic oxidative stress and the process persistence. In our opinion, further studies should focus on identifying the molecular mechanisms determining the heterogeneity of COPD progression, since it is known that in some patients the disease can progress rapidly, while other patients may remain relatively stable for many years.*

Keywords: *COPD, oxidative stress, antioxidant protection, proteinase inhibitory system, endogenous intoxication.*

Chronic obstructive pulmonary disease (COPD) is a persistent disease, with an estimated 384 million people suffer from COPD worldwide. According to a global

study by the World Health Organization COPD is the third leading cause of death in the world, involves of severe disability [8, 9].

Despite advances in the treatment of this pathology, COPD therapy is not always effective because of the disease progresses rapidly. Patients with COPD are manifested often exacerbations, reduced physical activity, impaired psycho-emotional state, a loss of social adaptation [3].

The main COPD indication is hypoxia and inflammation development. Oxidative stress is recognized as a major factor in COPD pathogenesis. There is free radical oxidation of lipids and proteins processes intensification on the background antioxidant protection decrease at inflammatory reactions activation. Imbalance in the proteinase-inhibitory system is of great importance in the development and course of the disease: it has been proved that COPD development is accompanied by proteolytic activation of blood plasma and the inhibitory potential weakening [6].

Exogenous non-enzymatic and enzymatic antioxidants are widely used to eliminate oxidative stress in the bronchopulmonary system. Such non-enzymatic antioxidants as glutathione (GSH), ascorbic acid and α-tocopherol are used commonly. Although oxidative stress is a trigger for COPD, antioxidants are not always effective [10,11].

Therefore, the aim of the presented work was to study the relationship between indicators of proteinase-inhibitory system, oxidative stress and endotoxicosis in patients with COPD.

MATERIALS AND METHODS

67 patients with COPD, men aged 36 to 59 years (mean age - 53.1±2.2 years), with a disease duration from 9.2 to 15.3 years (average - 12.5±1, 7 years) in the stable phase of the pathological process with II-IV degree of ventilation disorders according to the classification Global initiative for chronic obstructive pulmonary disease (GOLD) [4] were examined. The median value of forced expiratory volume in the first second after the test with a bronchodilator (FEV1) was 45.4 [43.7–47.1] % of the appropriate value in patients. The formulation of the clinical diagnosis of COPD was performed according to the Order of the Ministry of Health of Ukraine № 555dated 27.06.2013 [7]. All patients were in the stable phase of the disease for

at least two months. All subjects agreed to participate in the study. The study did not include patients with severe comorbidities of other organs and systems.

Examination of patients included general clinical methods (assessment of complaints, medical history, general history, physical examination data), assessment of clinical symptoms with the help of questionnaires (The Modified Medical Research Council Dyspnea Scale (mMRC)), COPD Assessment Test (CAT) [5]. Spirometry with FEV1 after a bronchodilator test to determine pulmonary ventilation was performed by computer spirometry on a MasterScreen Body / Diff (Jaeger, Germany). The control group consisted of 42 people (mean age - 54.0±2.1 years), which never smoked and as a result of clinical and laboratory studies were found healthy.

The content of lipid peroxidation (malonic dialdehyde (MDA), total antioxidant activity (TAOA)) [1], endotoxicosis (medium weight molecules (MSM)) [2], activity of proteinase (trypsin (T)) and inhibitor system (α1-antitrypsin (AT)) [6] in serum samples of patients with COPD and volunteers was determined.

The obtained results were processed using the program "Microsoft Office Excel" and "Statistica 6" by parametric and nonparametric statistics methods. To compare two independent groups of indicators, the t-test to determine the mean values (M) and standard error (± m) or the Mann-Whitney test (U) to determine the median (Me) and the upper and lower quartiles [25 - 75%]) were used. The relationship between the variables was estimated by the Spearman correlation coefficient (R). The probability of differences in relative indicators (data distribution) was determined by the criterion χ square ($\chi 2$). Significant differences between groups were considered at $p < 0,05$.

RESULTS AND DISCUSSION

The pathogenesis of COPD includes several pathogenetic links, such as oxidative stress, protease/antiprotease imbalance, apoptosis, endogenous intoxication, neurotoxic effects, but the relative contribution of each link among patients varies. Biochemical parameters of COPD patients compared with healthy volunteers were evaluated. It was shown that in patients with COPD MDA level was increased by 15% and in total antioxidant activity (TAOA) was decreased.

Activation of lipid peroxidation on the background of the antioxidant system inhibition worsens the condition of patients, which provokes a more severe course of COPD (table 1).

Table 1

Biochemical indexes in the serum at patients with COPD

	Control group n = 42	Patients with COPD n = 67
МДА, mol/mL	6,53 [5,72; 7,34]	9,90 [7,74; 12,06]
TAOA, mol/L	3,83 [3,27; 4,39]	2,51 [1,28; 3,74]
MCM, nm c.u.	0,26 [0,19; 0,33]	0,38 [0,29; 0,47]
AT, nm c.u.	5,40 [5,28; 5,52]	3,20 [2,69; 3,71]
T, nm c.u.	67,52 [53,62; 81,42]	251,20 [236,2; 266,20]

Oxidative stress is associated with the pathogenesis and progression of many acute and chronic respiratory diseases, including COPD. Oxidants generate airways inflammation, causing the production of pro-inflammatory cytokines, neutrophils, eosinophils, lymphocytes and macrophages, potentiating the action of histamine damaging tissues. According to the results of the study in patients with COPD, the level of MDA is increased, which can lead to injury to respiratory tract epithelium, while reducing bronchial tree mucous membrane protective ability.

Reduced overall antioxidant activity of serum was revealed in patients with COPD in the study. Disruption of oxidative-antioxidant balance activates resident cells in the lungs (epithelial cells and alveolar macrophages), generates chemotactic molecules that attract additional inflammatory cells and increase oxidative stress in the lungs. Together, these changes lead to a vicious circle of persistent inflammation, accompanied by chronic oxidative stress and persistence of the process.

Oxidative stress due to excessive activity of reactive radicals that can damage the structures of phospholipid membranes of cells of various organs, provokes acidosis changing the state of the body's buffer systems, disruption of proteolytic processes, and as a consequence, the appearance of intermediate decomposition products of proteins as such medium weight molecules (MSM) with toxic properties causing endogenous intoxication of the body. Defects in the mechanisms of tissue

repair and the development of endotoxicosis are characteristic for patients with COPD, as evidenced by the increase in MSM in the study. In patients with COPD MSM level exceeded the control index by 32 %. Pulmonary dysfunction reduces oxygen metabolism efficiency, which, in turn, causes hypoxemia, leading to the process progression in patients with COPD. Therefore, the MSM test can be used to monitor the effects of endotoxemia in the treatment and to describe disorders of cell membrane structures of patients with COPD.

Analyzing the state of the proteinase-inhibitory system in the serum, significantly activated trypsin (in patients with COPD, its activity exceeded the control group index on average by 3.7 times) against the background of probably low activity of its obligate inhibitor α1-AT was revealed.

Decreased antiprotease activity of α1-antitrypsin and increased trypsin activity leads to an imbalance in the proteinase inhibitory system and systemic inflammation development, which can accelerate apoptosis and tissue destruction and, as a consequence, the spread of proinflammatory mediators in the systemic circulation.

Determined phenomena result in complex metabolic disorders and nonspecific clinical manifestations of COPD.

CONCLUSION

In our view, further research should focus on identifying the molecular mechanisms determined the heterogeneity of COPD progression, as it is known in some patients the disease may progress rapidly, while others may remain relatively stable for many years. Therefore, new approaches to treatment are urgently needed to slow or even stop the manifestation of this disease and reduce mortality and disability.

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