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SYSTEMIC INFLAMMATORY MARKERS AND OVERWEIGHT IN PATIENTS SUFFERING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH III DEGREE OF BRONCHIAL OBSTRUCTION

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Summary. Chronic Obstructive Pulmonary Disease (COPD) is one of the most significant chronic pathological conditions in modern society and is widespread in both developed and developing countries. In recent years, the study of the development and course of COPD has been closely related to the identification of the role of immune imbalance, which is one of the leading factors in the development of chronic inflammation both in the bronchi and in the lungs. More and more attention is paid to the study of these disorders in different COPD phenotypes, particularly in combination with overweight, which is a well-studied risk factor for the development and rapid progression of a variety of chronic diseases, including respiratory tract pathology. The objective of the study was to determine the diagnostic significance of blood serum levels of CRP and TNF-α in exacerbation phase of COPD with III degree of bronchial obstruction in obese patients in order to improve management and treatment.

Key words. Chronic obstructive pulmonary disease, overweight, respiratory function, CRP, TNF-α.

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Chronic obstructive pulmonary disease (COPD) is among the most common pathologies of mankind and requires global resources for its early diagnosis and further effective treatment. Prevention and rational treatment of this pathology are considered as the priority tasks of modern pulmonology. According to existing concepts, COPD is a progressive heterogeneous disease characterized by persistent respiratory symptoms and airway obstruction due to pathological changes caused by the impact of harmful factors and is often combined with some co-morbid pathology that determines the prognosis, severity of the course, therapeutic approach and rehabilitation program [10, 11, 27]. This disease is the focus of attention primarily due to its progressive course, loss of productivity, high rates of disability and mortality.

Thuswise, in 1990 COPD was ranked 6th among all causes of death and in 2001 2.7 million people died of this disease that accounted for 5 % of all lethal cases all over the world [4, 12]. According to the data of the World Health Organization (WHO), COPD affects 210 million people and its incidence is expected to increase by 30 % in ten years (WHO, 2014). Furthermore, the key factor, which determinates the urgency of COPD issue, is its high treatment costs for both the health care system and society as a whole. The statistics of Global Initiative (GOLD, 2017-2018) shows that EU annual direct COPD costs reach 38.6 billion euros. Total COPD costs are three times higher than those for bronchial asthma [11, 20].

This pathology has an intricate non-fully-investigated multifaceted pathogenesis and episodic course with sequence of remission and exacerbation periods that are the most dangerous phase and determine the severity of the disease course. Frequent exacerbations dramatically increase medical expenses and have negative effect on the patients' quality of life, due to the escalation of COPD treatment regimens, specifically when hospitalization is necessary [17, 27].

Modern data prove that inflammation process, as the body's response to localized alteration, is the underlying cause of most diseases of lungs and bronchi, as it may be associated with not only bacteria or viruses, but also develop under the influence of substances of antigenic or haptenic nature, where the latter may lead to

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hypersensitivity to allergens that is the special vector of inflammation development [5, 6]. The initiation of inflammation in the sensitized organism is accompanied by marked microcirculatory disorders including exudation, edematization, leukocyte chemotaxis to the inflammation site and local proliferation of cellular elements [7, 8]. Local inflammatory process in COPD triggers systemic inflammatory reaction, which leads not only to the reduction of functional capacity of lungs, but also to the onset of systemic manifestations and outcomes, including depression, osteoporosis, endothelial dysfunction and cardiovascular diseases, loss of muscle mass and skeletal muscle dysfunction [23].

Until recently, the leading point of view was that nothing but the severity of bronchial obstruction influenced the COPD exacerbation rates [1, 3]. The relationship between the exacerbation rates and the severity of symptoms is demonstrated in conclusions of significant prospective studies [4, 9]. Much effort was devoted to the assessment of possible influence of extra-pulmonary factors on the increase of COPD exacerbation rates [2, 12]. It has been established that the course of disease in COPD patients may be exacerbated by some comorbid health conditions [15]. Comorbidity (Latin co — together, morbus — disease) is the presence of an additional clinical picture that already exists or may appear on its own, in addition to the already existing disease, and always differs from it, but may have some common pathogenetic links [25]. One of such conditions, which may have negative impact on COPD course, is excessive body weight, which is considered as one of the key problems of the 21st century and is among non-infectious diseases leading to the increase in morbidity and mortality rates, lost productivity and disability, and is a risk factor for the development and rapid progression of a variety of chronic diseases, including respiratory tract pathology [21, 25].

According to the WHO normal body mass index (BMI) is considered to be 18.5–24.9 kg/m², while the BMI 25.0–29.9 kg/m² is considered as overweight [22, 24]. Possible mechanism of weight gain, with parallel loss of muscle mass in COPD patients, may be associated with the decrease in physical activity due to exertional dyspnea, prolonged use of systemic glucocorticosteroids with the development of immunosuppressive effects at late stages of disease progression [28]. However, it is known that the COPD course itself is accompanied by significant immune disorders, including cytokine profile. Known data prove that the manifestations of systemic effects at early stages of COPD development may occur prior to records of clinically significant episodic increase of markers of proinflammatory activation in peripheral blood [13, 14]. Inflammatory reaction is a complex mechanism involving many cells and molecules, where cytokines basically ensure the sequence and completeness of immune response [5, 18]. Specifically the peculiarities of chronic inflammatory reaction determine the nature and course of COPD, rate of progression of pathological changes and response to therapy [8, 22]. One of the components of such Th1-type chronic inflammatory response is neutrophil inflammatory process characterized by an increase in neutrophils, macrophages and T-lymphocytes. These inflammatory cells are able to release various cytokines and mediators (IL-1, IL-6, IL-8, TNF-α, granulocyte-macrophage colony-stimulating factor, soluble intercellular adhesion molecule-1), which are the key components of balance of inflammation progression and, consequently, the pathology [13, 19]. These biologically active compounds can cause endothelial activation, increase further expression of adhesive molecules, accompanied by subsequent release of low-molecular-weight inflammatory mediators — histamine, prostaglandins, which generalize the development of inflammatory reaction [14, 26].

It is known that COPD is accompanied by activation the system of antioxidant protection and acute-phase proteins, namely — C-reactive protein (CRP), which appears in blood plasma within 4–6 hours after the injury. CRP performs several functions at once: mediatory, transportational and immunomodulatory. It activates the complement system, stimulates lipoprotein uptake by macrophages, blocks synthesis of inflammatory mediators through the binding effect of phospholipid membranes, however, at the same time, it increases leukocyte adhesion to the endothelium, thus intensifying the inflammatory cascade [3, 5].

Currently, the confirmed fact is that CRP may be used as activation marker for bacterial infections in COPD exacerbation, as well as the fact that the increase of CRP levels in COPD patients is an independent predictor of the progression of bronchoconstriction, development of respiratory failure, cardiovascular disease and mortality [1, 13]. However, literature reports do not show firm agreement regarding the possible use of CRP and different cytokines in destabilization of the course and development of exacerbation phase in COPD patients on the background of overweight. Although, it has been established that overweight is accompanied by latent inflammation of adipose tissue, with fatty acid metabolism products stimulating the migration of macrophages and other immunocompetent cells into the adipose tissue [1, 22], that produces more than 50 adipokines, which in their turn affect the metabolism of lipids, inflammatory processes and immune system [22].

In order to determine the value of CRP as a biomarker for systemic inflammation or severity of COPD, its serum content was compared with proinflammatory cytokines, particularly TNFα, which is produced predominantly by mononuclear phagocytes and activated T-lymphocytes and belongs to the family of tumor necrosis factors. TNFα is considered to be the key proinflammatory cytokine and acute-phase protein, and also takes part in the chronization process, by means of both promotion of the adhesion of macrophages and, indirectly, due to the platelet-activating factor [25, 26]. Localization and severity of chronic inflammation, its nature and peculiarities of trigger mechanisms determine the specific character of pathological process and clinical symptomatology, while the COPD progression rate is also a marker of adequate therapy and prognosis [22, 23].

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A number of scientific studies have been carried out in order to study the role of proinflammatory cytokines in the development and course of COPD in Ukraine and other countries. For example, we are familiar with scientific works that demonstrate the value of these indicators as the predictive markers for COPD in patients with hypertension associated with overweight [16] and bronchial asthma in combination with obesity [2]. However, the issue on the role of proinflammatory cytokines and CRP in the process of generalization of the inflammatory response with the decrease of FEV_1 indices below 50 % in obese patients still remains undefined.

The objective of the study was to determine the diagnostic significance of blood serum levels of CRP and TNF-α in exacerbation phase of COPD with III degree of bronchial obstruction in overweight patients in order to improve management and treatment.

Materials and methods

The verification of the diagnosis of COPD and its formulation was carried out in accordance with the Order of the Ministry of Health of Ukraine № 555 from June 27, 2013 "On approval and implementation of medical-technological documents on standardization of medical care in chronic obstructive pulmonary disease". Patients being in a stable phase of the process received baseline therapy in accordance with the currently valid Order of the Ministry of Health of Ukraine № 555 from June 27, 2013, which involved the use of long-acting bronchodilators, inhalational and/or systemic glucocorticosteroids, and, if necessary, short-acting bronchodilators [14].

The main treatment group involved 45 patients suffering from COPD with III degree of bronchial obstruction (male patients — 37 (75.6 %), female patients — 11 (24.4 %) with obesity); the average age was (61.9 ± 3.1) years. They were divided into subgroups depending on the phase of their pathology: subgroup I included 18 patients (40 %) with stable phase of pathological process, subgroup II involved 27 patients (60 %) at exacerbation phase. The experimental group consisted of 67 COPD patients with III degree of bronchial obstruction (male patients — 51 (76. 1 %), female patients 17 (25.4 %) with normal body weight); average age — (62.9 ± 2.8) years. They were also divided into subgroups depending on the phase of their pathology: subgroup I included 25 patients (37.3 %) with stable phase of pathological process, subgroup II involved 42 patients (62.7 %) at exacerbation phase.

The control group involved 23 apparently healthy individuals (AHI) representative by sex and age, without any signs of pulmonary diseases or other pathologies of internal organs, 12 of them were overweight. The investigation was performed in the phase of remission and at the time of verification of the development of exacerbation phase. All the surveyed patients gave their consent to participate in clinical trial.

The average duration of the disease in patients with COPD III degree of bronchial obstruction was (26.8 ± 1.4) years in those with obesity, and (31.4 ± 1.2) years in patients with normal body weight. Among the existing risk factors, which triggered the COPD development in both main treatment group and comparison group, tobacco smoking was prevalent: 29 individuals (64.4 %) with average smoking history of (17.8 ± 2.1) pack-years and 48 individuals (71.6 %) with average smoking history of (19.9 ± 2.2) pack-years.

Computed spirometry with the help of "SpiroCom medic" (KhAI, Kharkiv, Ukraine) was used to study the indices of respiratory function with indicators of main bronchoobstructive indices (forced vital capacity (FVC) of lungs, forced expiratory volume (FEV_1)). The levels of systemic inflammatory markers were determined by quantitative methods in blood serum: TNF-α, using ELISA kits (Dialcone, France). The serum CRP level was determined by a semi-quantitative latex agglutination method using the Dialab reagent kit (Austria).

Statistical processing of research materials was carried out using biometric analysing methods implemented in software packages EXCEL-2003 (№ 74017641-9475201-57075) and STATISTICA 6.0 (№ 31415926535897). The assessment of statistical significance of mean values for independent samples was performed by means of Student's and Mann-Whitney tests, while dispersion was evaluated with Fisher's test. The difference between the comparative values was considered to be significant at $p < 0.05$, while the tendency of changes was indicated in the range of $0.05 < p < 0.10$, with the index rate calculated to the tenth place.

Research findings and their discussion:

The values of main spirometric indices of respiratory function in the main treatment group and the comparison group were identical (Table 1).

We have observed the increase of TNF-α and CPR levels in blood serum of patients with COPD III degree of bronchial obstruction with normal body weight in the remission phase as compared with the control group, namely 1.4 ($p < 0.05$) and 2.3 times ($p < 0.05$), respectively. These indices were 1.3 ($p < 0.05$) and 2.6 times ($p < 0.05$) higher in the exacerbation phase than the same indices of the comparison group in the remission phase, and 1.9 ($p < 0.05$) and 6.1 ($p < 0.05$) times higher

Table 1. Indices of respiratory function (%) in COPD patients with III degree of bronchial obstruction in relation to the body weight, (M ± m)

Indices in subgroups of examined patients	Rated values	
	Phase of remission	Exacerbation phase
FEV_1 (%)		
Main treatment group, (n = 45)	40.2 ± 3.1	33.3 ± 3.0
Comparison group, (n = 67)	45.5 ± 3.4	38.4 ± 3.2
FVC (%)		
Main treatment group, (n = 45)	67.3 ± 3.0	62.6 ± 3.6
Comparison group, (n = 67)	72.6 ± 3.7	69.1 ± 3.1
FEV_1/FVC		
Main treatment group, (n = 45)	55.2 ± 3.2	53.4 ± 3.1
Comparison group, (n = 67)	57.5 ± 3.8	57.1 ± 3.0

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Таблиця 2. Рівень CRP, TNF-α, ШОЕ у обстежених хворих на ХОЗЛ із III ступенем бронхообструкції в залежності від маси тіла, (M ± m)

Indices	Main treatment group		Control group, n = 12	Comparison group		Control group, n = 11
	Subgroup I Phase of remission, n = 18	Subgroup II Exacerbation phase, n = 27		Subgroup I Phase of remission, n = 25	Subgroup II Exacerbation phase, n = 42	
TNF-α, pg/ml	207.7 ± 18.1*°	265.8 ± 22.3#°	113.2 ± 13.6	133.9 ± 11.9*	178.8 ± 10.9#	95.3 ± 12.5
CRP, mg/l	12.4 ± 1.5*°	20.6 ± 1.9#°	5.1 ± 1.3	6.6 ± 0.4*	17.1 ± 1.0#	2.8 ± 0.3
ESR, mm/hr	17.8 ± 2.7*°	22.5 ± 2.0#°	11.7 ± 3.1	12.9 ± 3.0*	17.3 ± 2.5#	9.7 ± 3.2

Note: * — statistically significant difference compared with the control group ($p < 0.05$); # — statistically significant difference between levels in the phase of remission and in the phase of exacerbation of the pathology ($p < 0.05$); ° — statistically significant difference compared with the corresponding indices in the comparison group patients ($p < 0.05$).

than the corresponding indices in the control group patients, respectively.

Increased serum levels of CRP and TNF-α were more pronounced in patients with excessive body weight, particularly in case of destabilization of clinical course of the disease. Thus, we observed an increase in the serum levels of TNF-α and CRP in the exacerbation phase compared with the remission phase, namely, 1.3 times ($p < 0.05$) and 1.7 times ($p < 0.05$), respectively, and 2.3 times ($p < 0.05$) and 4.0 times ($p < 0.05$) than the corresponding values in the control group patients. In the phase of exacerbation of the pathology, the level of these indicators was higher by 1.5 times ($p < 0.05$) and 1.2 times ($p < 0.05$) compared to values of the same indicators of the comparison group.

The evaluation of blood serum levels of TNF-α and CRP in relation to the body weight of obese patients in the remission phase showed that these indices were 1.6 ($p < 0.05$) and 1.9 times ($p < 0.05$) higher than the corresponding indices in the comparison group patients, and even more pronounced changes were observed in the phase of exacerbation, where these indices in patients of the main treatment group exceeded the indices obtained in the comparison group by 1.5 ($p < 0.05$) and 1.2 times ($p < 0.05$), respectively.

We have also observed an increase of ESR level in COPD patients with III degree of bronchial obstruction with overweight, where this index in the exacerbation phase was 1.9 times ($p < 0.05$) higher than the indices of the control group, 1.3 times ($p < 0.05$) higher than its index in the remission phase and 1.3 times ($p < 0.05$) higher than that of the comparison group in the exacerbation phase, respectively. So, overweight contributes to a more severe course of the disease.

Conclusions

Overweight is a factor promoting rapid COPD (III degree of bronchial obstruction) progression, which is evidenced by 1.2 times shorter duration of the disease ($p < 0.05$) with parallel 2.1 pack-years shorter cigarette smoking history.

It has been established that in the remission phase excessive body weight of COPD (III degree of bronchial obstruction) patients was associated with the increase of serum levels of CRP by 1.9 times ($p < 0.05$), TNF-α — by 1.6 times ($p < 0.05$) and ESR — by 1.4 times ($p < 0.05$), as compared with the corresponding indices observed in patients with normal body weight, which indicates that excessive body weight leads to a more severe course of the pathology.

The development of COPD exacerbation phase (III degree of bronchial obstruction) in patients with excessive body weight is accompanied by significant increase in the levels of CRP by 21.9 % and TNF-α by 39.8 %, as compared with those of patients with normal body weight, and these changes correlated with the increase in ESR levels for TNF-α ($r = 0.92$; $p < 0.05$) and CRP ($r = 0.97$; $p < 0.05$), respectively. These data suggest that excessive body weight is a predictor of faster progression of pathology.

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