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LUNG FUNCTION TESTING ACCORDING LEPTIN LEVELS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract. Chronic obstructive pulmonary disease (COPD) belongs to urgent medical and social problems of our time. Prognosis of COPD is often determined by a comorbidity, in particular obesity. The key chain, which unites COPD and obesity, is systemic inflammation, in the development of which the hormone of fatty tissue leptin plays an important role. The presence of receptors to leptin in the alveolar and bronchial epithelial cells, in smooth muscle tissue and submucous bronchial membrane allowes to assume that leptin takes pathogenetic part in COPD progression. The **aim** of our research was to estimate the leptin level in COPD patient and analyze changes of the respiratory function depending on it. **Methods.** We have been examined 26 patients with exacerbation of COPD (13 male and 13 female, 58 y.o.) and 20 healthy people

representative by gender, age and body mass. The level of serum leptin has been defined by the solid phase enzyme linked immunosorbent analysis, lung function – by computed testing. **Results and conclusion.** With the leptin level increase all of the lung function parameters progressively decreased, most significant - forced vital capacity and peak expiratory flow. Patients with hyperleptinemia had significantly lower measurements of forced expiratory volume in 1 second and vital lungs capacity. Severe degree of both obstructive and restrictive changes has been found more often among patients with hyperleptinemia and leptin level has been associated with the bronchial obstruction severity.

Key words: leptin, hyperleptinemia, lung dysfunction tests, chronic obstructive pulmonary disease.

Introduction. Chronic obstructive pulmonary disease (COPD) belongs to urgent medical and social problems of our time, that defines the necessity of a research of new ways of an elimination of risk factors, timely and qualified diagnosis, and effective treatment [2]. The severity of a COPD progression and its prognosis are often determined by a comorbidity, in particular obesity, its frequency among COPD patients reaches up to 54% and significantly exceeds the prevalence in the population [3]. To the key chain, which unites COPD and obesity, systemic inflammation is referred, in which a the hormone of fatty tissue leptin plays an important role. A significant vascularization of lungs, the presence of receptors to leptin in the alveolar and bronchial epithelial cells, in

smooth muscle tissue and submucous bronchial membrane, and also the increase of leptin levels in sputum of patients with severe exacerbations of COPD allowed to assume that leptin takes a pathogenetic part in disease progression [5,6]. Leptin also promotes the mucin production by respiratory epithelial cells that leads to the hypersecretion [11], stimulates the inflammatory mediators synthesis, in particular interleukin-6 which promotes the increase of the thickness of the membrane, subepithelial fibrosis, hypertrophia and proliferation of bronchial smooth muscle tissue [7]. Leptin blocks apoptosis of T-lymphocytes in the submucous tissue of bronchus [1] and supports inflammatory processes due to the neutrophils and macrophages activation, releasing of free radicals, stimulation of leukotrienes and prostaglandins synthesis [9].

Leptin level increase is considered as a biomarker of the emphysematous COPD phenotype [8] and lung restriction in children or adolescents with obesity [4]. The increase of level of leptin in people with asthma has been associated with the decrease of vital capacity (VC), its accelerated value (forced vital capacity; FVC), peak expiratory flow rate (PEF) [10], although data about COPD is incomplete what determines the topicality of our research.

Aim: to estimate the leptin level in COPD patients and analyze changes of lung function parameters according it.

Materials and methods. We have been examined 26 patients with COPD exacerbation (13 male and 13 female, the median of an age is 58 y.o.). The control group has consisted of 20 healthy people representative by gender, age and body mass. The level of serum leptin has been defined by solid phase enzyme linked immunosorbent analysis with the reagent «DRG Leptin ELISA» (Germany), the normal range is 2.05-5.63 ng/ml for men and 3.63-11.09 ng/ml for women. The body mass has been considered normal when body mass index

(BMI) is 18-24.9 kg/m^2, overweight - 25-29.9 kg/m^2, the obesity has been diagnosed in BMI>30 kg/m^2. Lung function was checked with computed spirography («Pneumoscreen»). Results have been processed by methods of variation statistics (Statistica 6,0), demonstrated as a median[lower; upper quartile], correlations have been estimated by Kendall (τ) analysis.

Results and discussion. The general content of leptin in patients with COPD was 12.0[1.4;20.6] ng/ml what is significantly higher than in the control group (6.9[1.9;9.3] ng/ml; p<0.01). The level of leptin depended on the body mass. Thus, among patients with normal body mass (n=10) the level of leptin was 1.5[0.9;8.6] ng/ml, that is significantly lower than among patients with overweight (n=6; 24.7[14.0,40.0]; p=0.007) and obesity (n=10; 25.9[10.8;45.9]; p=0.0007). According correlative analysis the level of leptin expectedly directly correlated with BMI (τ=0.5; p=0.0006), the stronger correlation was revealed among men (τ=0.6; p=0.005). Frequency of hyperleptinemia has reasonably been increased among patients with obesity, than among persons with normal body mass (90.0±9.5% vs. 30.0±14.5%; p<0.01). It is important that conducted Kendall correlative analysis has shown that in all patients with COPD the leptin level was strictly associated with both volumetric and speed lung function criteria: FVC (τ=-0.4, p=0.007), VC (τ=-0.3, p=0.02), PEF (τ=-0.3, p=0.04), and directly - with the severity of bronchial obstruction (τ=0.3; p=0.01).

According to the leptin content all patients have been divided into two groups: a normal level of leptin has been observed in 31% of patients with COPD (1st group) and increased - in 69% (2nd group). The groups do not substantially differentiate by age, gender, clinical presentations (all p>0.05), but the difference was in BMI (23.0[20.7;23.8] kg/m^2 vs. 30.5[27.0;35.1] kg/m^2, p=0.0005).

It is important that the level of serum leptin distinctly been associated with

the lung function parameters. Analysis of relative criteria of respiratory function show that increase of leptin level was associated with all criteria decreasing with maximum intensity in the key screening tests – the volume of forced expiratory volume per 1 second (FEV_1) and VC (table 1). This can prove more severe obstructive and restrictive lung function impairment in the condition of hyperleptinemia. Attention is also paid to the clear tendency to the decrease of other results of respiratory flow: FVC, PEF and maximal expiratory flow on the 75% of FVC levels (MEF_{75}) in 2nd group (the difference is statistically substantial).

Table 1. The lung function parameters in patients with COPD with normal (1st group) and increased (2nd group) leptin levels

Parameters	1st group	2nd group	p
FVC, %	75.4[72.2;90.0]	62.3[45.4;75.8]	0.07
VC, %	85.3[73.3;89.4]	63.2[45.6;77.0]	0.008
FEV_1, %	64.4[60.3;92.9]	48.0[33.6;73.4]	0.04
FEV_1/FVC, %	70.2[60.3;94.1]	74.0[54.1;84.6]	>0.05
FEV_1/VC, %	66.7[59.5;70.7]	61.5[50.8;82.0]	> 0.05
MEF_{25-75}, %	62.2[30.1;76.2]	33.9[22.3;60.2]	>0.05
PEF, %	63.4[48.6;85.8]	48.7[36.2;56.3]	0.06
MEF_{25}, %	43.3[30.0;56.2]	38.8[23.9;53.1]	>0.05
MEF_{50}, %	58.8[30.3;80.8]	29.8[21.0;56.3]	>0.05
MEF_{75}, %	82.4[46.0;107.1]	48.0[31.0;70.8]	0.051

Remarks: MEF_{25-75} - middle expiratory flow during period 25-75 % FVC, $MEF_{25,50,75}$ – maximal expiratory flow on the 25, 50, 75 % FVC levels.

It has also been found that a severe stage of pulmonary obstruction (FEV_1 <49%) has been met significantly more frequently among patients with hyperleptinemia (52.9±12.1% vs. 11.1±10.5%; $p<0.05$). It is important that the most severe stages of both restrictive (VC<50%) and obstructive (FEV_1<30%) changes have been diagnosed exclusively among patients with hyperleptinemia (23.5%, $p<0.05$; and 11.8%, $p>0.05$).

It should be noted that in patients with normal leptin level indicators of

lung function showed moderate bronchial obstruction, while in patients with hyperleptinemia tests VC, MEF_{25-75} and MEF_{75} have been significantly reduced, what together with other lung function tests can point to generalized mixed obstructive nature of the lung function with the potent restriction. The significant decrease in VC, which we have seen in the 2nd group patients, can be explained by the absolute reduction in the number of functioning lung tissue, and by loss of elastic lung properties (emphysema). In some cases, mild reduction of VC due to bronchial obstruction can be caused by reduction of expiratory reserve volume. However, the detection of restrictive violations provides the defining of total lung capacity that requires further investigation. The fact that MEF_{75} was lower than normal just in patients with hyperleptinemia may indicate presence of bronchial obstruction in small-size bronchi, what on the other hand, can be potentiated by emphysematous changes in the lungs with the reduction of lungs elasticity.

As far as we are concerned, the pathogenetic role of leptin in the course of COPD is not limited by its inflammatory influence, but it is associated with progressive functional abnormalities of lung ventilation also. The results of our research point to the negative impact of hyperleptinemia on bronchobstructive syndrome progression in patients with COPD. The expression of leptin by cells of alveolar wall and participation of it in the development of emphysema can explain the reduction of VC in patients with hyperleptinemia and COPD what has been found by us.

Conclusions: among patients with COPD the level of serum leptin has significantly exceeded the content among healthy people ($p<0.01$). The increase leptin level among patients with COPD with overweight and obesity in comparison with patients with normal body mass (both $p<0.01$) has been found. Among patients with hyperleptinemia the decrease of all lung function criteria

was established but more significantly of FEV_1 and VC. As severe degree of obstructive and restrictive changes has been found more often among patients with hyperleptinemia and its level was strictly associated with the bronchial obstruction level, the increase of leptin level can be a biomarker of difficult abnormalities of respiratory function.

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