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CLINICAL AND LABORATORY PECULIARITIES IN PATIENTS WITH COPD AND ASTHMA DEPENDING ON BMI

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Abstract:

The purpose of the study was to assess the effect of body weight on the course of COPD and asthma. Material and Methods: The clinical phase of the study was conducted on 113 patients with asthma and 264 patients with COPD. The patients were divided into 3 groups within their nosology depending on their BMI: with normal body weight (BMI: 18.5-24.99), overweight (BMI: 25-29.99) and obesity (BMI: 30 or more). At the first stage of the study, an individual registration card was filled out for each patient. The symptoms of asthms and COPD were objectified by using a 10-point visual analogue scale. To assess the severity of shortness of breath, a 4-point mMRC scale was used. The severity of symptoms of COPD and the impact of the disease on the daily activities of patients was assessed using the COPD Assessment Test. To assess the symptoms of COPD over the past week, a clinical questionnaire for COPD has been used - The Chronic obstructive pulmonary disease Control Questionnaire. To assess the degree of asthma control, an Asthma Control Test was used. The "Quality of Life for Asthma Patients" was used to assess the quality of life of patients with asthma, and for patients with COPD - Short Form Medical Outcomes Study 36. All patients underwent spirometry. The study of specific markers in blood serum was performed; in this research work have been analysed levels of leptin, adiponectin, the degree of total oxidative damage (TOD), the total antioxidant status (TOS), IL-4, IL-6, TNF-α, neuropeptide Y. All received data were compared with the severity of clinical symptoms. The data were processed statistically using standard computer programs. The data obtained allow us to conclude that obesity as a source of chronic systemic inflammation is a predictor of the adverse course of asthma and COPD. To numerically determine the effect of obesity on these pulmonological pathologies, the following serum indices can be used: leptin, resistin, TNF-α. In addition, for asthma, in particular, neuropetid Y, the total oxidative damage and the total antioxidant status are promising markers.

Key words: *asthma, COPD, BMI, neuropeptide Y.*

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INTRODUCTION:

Asthma and chronic obstructive pulmonary disease (COPD) are the main issues of modern pulmonology, attracting scientists to search for methods of their prevention and treatment. In total, more than 500 million people in the world suffer from asthma and COPD. (1.2) In recent years, the scientific community has been particularly interested in studying these pulmonary diseases in combination with concomitant pathology, including obesity. (3,4,5)

The study of the combination of asthma with obesity was reflected in the formation of a new phenotype of the disease “asthma with obesity”, while the effect of body weight on COPD was considered in less detail. (6.7) However, the pathological processes connecting these two diseases are not completely known. (8)

THE AIM OF THE STUDY:

to assess the levels of leptin, asthmaiponectin, the degree of total oxidative damage (TOD), the total antioxidant status (TOS), IL-4, IL-6, TNF-α, neuropeptide Y, as well as the severity of clinical symptoms in patients with asthma and patients with COPD in various BMIs groups, and analyse the results when comparing with spirometry parameters.

MATERIAL AND METHODS:

The clinical part of the study was conducted on the basis of the general acute hospital №1 in Voronezh. Biochemical analyses were carried out on the basis of the Research Institute of Experimental Biology and Medicine of VSMU named after N. N. Burdenko of the Ministry of Health of Russia.

For the final analysis, data were obtained on 113 patients with asthma: 27 men and 86 women aged 18 to 75 years (average age was 57.81 ± 13.05 years) and 264 patients with COPD: 196 men aged 43 to 72 years (average age 63.94 ± 6.42 years) and 68 women from 46 to 70 years (average age 60.66 ± 7.82 years).

The diagnosis of asthma was masthmae in accordance with the criteria of the GINA 2018, the diagnosis of COPD was masthmae in accordance with the GOLD 2017.

Regarding the BMI parameter, all patients were divided into three groups within their nosology. Thus, the following groups were obtained: group 1 included patients with asthma and normal body weight (BMI: 18.5-24.99), group 2 - with asthma and overweight (BMI: 25-29.99), 3 group - with asthma and obesity (BMI: 30 or more). Similarly, groups of patients with COPD were formed: group 1 - patients with a diagnosis of COPD and normal body weight (BMI: 18.5-24.99), group 2 - with COPD and overweight (BMI: 25-29.99) , group 3 - with COPD and obesity (BMI: 30 or more).

Exclusion criteria were the patient's refusal to participate in this study; exacerbation of asthma and COPD; acute and chronic neurological, psychiatric and endocrinological disorders at the time of examination; chronic diseases in the acute stage; severe and decompensated diseases of the liver and kidneys; severe and decompensated cardiovascular diseases (acute period of myocardial infarction, unstable angina, transient ischemic attack, intracerebral hemorrhage, acute heart failure, etc.); malignant neoplasms; multiple organ failure of various origins; pregnancy and lactation; severe infectious diseases.

At the first stage of the study, an individual registration card was filled out for each patient. The symptoms of asthms and COPD were objectified by using a 10-point visual analogue scale (VAS). To assess the severity of shortness of breath, a 4-point mMRC (modified Medical Research Council) scale was used. The severity of symptoms of COPD and the impact of the disease on the daily activities of patients was assessed using the COPD Assessment Test (CAT). To assess the symptoms of COPD over the past week, a clinical questionnaire for COPD has been used - The Chronic obstructive pulmonary disease Control

Questionnaire (CCQ). To assess the degree of asthma control, an Asthma Control Test (ACT) was used. The "Quality of Life for Asthma Patients" (international counterpart: Asthma Quality of Life Questionnaire - AQLQ) was used to assess the quality of life of patients with asthma, and for patients with COPD, a validated non-specific general short health status assessment questionnaire - Short Form Medical Outcomes Study 36 (SF-36).

To conduct a spirometry study, a Diamant-S spirometer was used (CJSC "Diamant", Russia).

The study of specific markers in blood serum was performed on a "Multiskan Go" analyzer (Thermo Fisher Scientific, Finland). The tablet was washed using a tablet-washer for Wellwash enzyme-linked immunosorbent assay (Thermo Fisher Scientific, Finland), incubation (if necessary) using a PST-60HL-4 thermal shaker (Biosan, Latvia).

Statistical data processing was performed using the STATGRAPHICS 5.1 Plus for Windows software package.

The study was approved by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko. Written informed consent was obtained from all patients participating in the study.

RESULTS:

The data obtained during the study show that 37 people (asthma and normal body weight) were assigned in 1 group of patients with asthma, the 2 group consisted of 38 people (asthma and overweight); Group 3 - 38 people (asthma and obesity). Patients with COPD were divided as follows: group 1 - 88 patients (COPD with normal body weight), group 2 - 88 patients (COPD with overweight), group 3 - 88 patients (COPD and obesity). These study groups did not significantly differ in a number of socio-demographic indicators and, therefore, could be used for a comparative assessment.

Significant differences were revealed among the symptoms of asthma, the severity of which patients independently assessed according to the VAS scale between the three studied groups.

Self-assessment of the cough severity was significantly different in groups 2 and 1 ($F = 8.34$; $p = 0.0000$), as well as 2 and 3 ($F = 4.47$; $p = 0.0379$), while between groups 1 and 3 significant differences were not detected ($F = 0.41$; $p = 0.5218$). Significant differences in the self-assessment of the severity of dyspnea were observed between groups 1 and 3 ($F = 4.09$; $p = 0.0467$). When analyzing the self-assessment of the severity of viscous sputum among the three studied groups, there were no significant differences ($F = 3.66$; $p = 0.0597$), ($F = 3.09$; $p = 0.0829$), ($F = 0.14$; $p = 0.7070$). Self-esteem of labored breathing significantly differed among patients of groups 1 and 2 ($F = 6.96$; $p = 0.0103$), while differences between groups 1 and 3, as well as between groups 2 and 3 were not significant for this indicator ($F = 2.17$; $p = 0.1456$), ($F = 0.82$; $p = 0.3684$).

According to the results of ACT in 3 groups of patients (patients with asthma and obesity), the level of disease control was significantly lower compared to group 2 (overweight) ($F = 6.04$; $p = 0.0165$). There were no statistically significant differences between groups 3 and 1, 2 and 1 ($F = 3.67$; $p = 0.0594$), ($F = 0.90$; $p = 0.3454$).

When analysing the quality of life of patients with asthma in all three groups (with normal, overweight and obesity), higher rates were noted in the domain of asthma symptoms (51.35 ± 14.06, 48.05 ± 8.35 and 47, 61 ± 13.00 points, respectively), the domain of "activity limitations" (52.49 ± 13.54, 49.79 ± 11.08 and 45.53 ± 12.14 points, respectively) and lower in the domains "emotional sphere "(21.43 ± 19.9, 19.11 ± 17.6, 19.13 ± 17.63 points, respectively), "environmental impact "(16.05 ± 6.78, 14.84 ± 3 , 61 and 13.68 ± 4.95 points, respectively). There were no statistically significant differences between groups with normal body weight, overweight and obesity in the domains of "asthma symptoms", "activity restriction", "emotional sphere", and "environmental impact" ($F = 1.08$; $p = 0$, 3439), ($F = 3.07$; $p = 0.0506$), ($F = 1.52$; $p = 0.2233$), ($F = 1.90$; $p = 0.1542$).

Spirometry study showed significant differences in bronchial obstruction in patients with asthma with different body weights.

So, for instance, in the group of patients with asthma and normal body weight, the following indicators were significantly higher compared with the groups with overweight and obesity, which were: FEV1 - 89.30 ± 23.27 ($F = 7.42$; $p = 0$, 0013), FVC - 104.10 ± 23.32 ($F = 9.19$; $p = 0.0004$), VC - 93.08 ± 5.18 ($F = 22.49$; $p = 0.0000$). Significantly lower in the group of patients with asthma and overweight compared with groups with normal body weight and obesity was the following indicators: FEV1/FVC - 76.87 ± 17.86 ($F = 7.46$; $p = 0.0011$), MEF25, - 41.35 ± 30.42 ($F = 6.36$; $p = 0.0029$), MEF50 - 37.39 ± 32.68 ($F = 4.13$; $p = 0.0202$), PEF - 15.12 ± 10.67 ($F = 7.70$; $p = 0.0015$).

The average values of interleukin-4 were 6.32 ± 3.08 pg / ml, 6.40 ± 3.51 pg / ml, 6.89 ± 5.40 pg / ml in groups 1, 2 and 3, respectively. Significant differences in the level of interleukin-4 in groups with normal body weight, overweight and obesity were not detected (F = 0.21; p = 0.8085). The average values of interleukin-6 were 20.86 ± 13.93 pg / ml, 17.16 ± 9.16 pg / ml, 14.92 ± 9.80 pg / ml in the first, second and third groups, respectively. The differences in the study groups for interleukin-6 were not significant (F = 2.71; p = 0.0708).

The values of the TOS were 535.78 ± 64.35 μmol / L, 277.59 ± 63.49 μmol / L and 287.96 ± 63.49 μmol / L in the first, second and third groups, respectively. The value of the TOS characterizing the antioxidant activity of the body was significantly higher in the first group of patients compared with the second and third groups (F = 5.21; p = 0.0069).
The values of the TOD to the molecules were 877.70 ± 623.33 μmol / L, 1177.75 ± 1022.51 μmol / L and 1454.69 ± 1257.72 μmol / L in the first, second

and third groups, respectively. The values of this indicator in the first group of patients were significantly lower than in the third group (F = 3.09; p = 0.0496).

The level of TNF-α was significantly lower in group 2 (1.78 ± 0.35 pg / ml) compared with the 1 (2.01 ± 0.31 pg / ml) and 3 (2.03 ± 0.37 pg / ml) by groups (F = 8.69; p = 0.0043), (F = 8.97; p = 0.0037), respectively. There were no statistically significant differences in the level of TNF-α between the first and third groups (F = 0.08; p = 0.7821).
The level of neuropeptide Y was 0.31 ± 0.02 ng / ml in the first group, 0.48 ± 0.02 ng / ml in the second group, 1.19 ± 0.25 ng / ml in the third group of patients. The value of neuropeptide Y was significantly lower in group 1 with normal body weight compared with group 2 with overweight and group 3 with obesity (F = 36.69; p = 0.0000), (F = 8.97 ; p = 0.0037). There were no statistically significant differences in the level of neuropeptide Y between the second and third groups (F = 0.08; p = 0.7821).

The leptin level was significantly higher in group 3 (patients with asthma and obesity) compared with group 1 (patients with asthma and normal body weight) and group 2 (patients with asthma and overweight) and amounted to 13.01 ± 1.97 , 11.32 ± 1.99 and 22.36 ± 1.97 ng / ml, respectively (F = 9.06; p = 0.0002). The adiponectin level was 23.66 ± 11.03 μg / ml in the first group, 23.40 ± 11.29 μg / ml in the second group and 23.70 ± 10.25 μg / ml in the third group of the studied. There were no statistically significant differences in adiponectin levels in groups with normal body weight, overweight and obesity (F = 0.01; p = 0.9915). The resistin level was 5.40 ± 2.63, 5.83 ± 2.42 and 6.86 ± 3.36 in the first, second and third group of patients, respectively. Differences in resistin levels in the study groups were statistically significant (F = 3.61; p = 0.0384).

In patients with COPD and obesity, the severity of dyspnea, sputum production and general weakness according to VAS was significantly lower compared to patients with COPD and normal body weight. (F = 25.33, p = 0.0000), (F = 5.80, p = 0.0170), (F = 8.52, p = 0.0040) and amounted to 7.14 ± 2.32 , 3.97 ± 1.86 and 6.66 ± 2.06 points, respectively. With a comparative characteristic of the severity of symptoms in patients with COPD and overweight, the severity of dyspnea according to VAS was significantly lower compared with patients with COPD and normal body weight and amounted to 8.0 ± 1.72 and 8.60 ± 1.44 points, respectively (F = 6.32, p = 0.0128). There were no statistically significant differences between the groups in terms of VAS cough, VAS sputum, VAS weakness (F = 0.24, p = 0.6274), (F = 1.24, p = 0.2664), (F = 2, 36, p = 0.1267).

When analysing the parameters of spirometry, indicators such as FEV1, FVC and FEV1/FVC in patients with COPD and obesity, as well as in patients with COPD and overweight, were significantly higher than in patients with COPD with normal body weight (F = 39.78, p = 0.0000), (F = 38.54, p = 0.0000), (F = 24.80, p = 0.0000) for comparing groups 1 and 3, and (F = 10.13, p = 0.0017), (F = 5.60, p = 0.0191), (F = 23.18, p = 0.0000) for comparing 1 and 2.
Based on the results of spirometry, groups 1 and 3 also significantly differed in the distribution of patients according to the degree of bronchial obstruction (GOLD 1, 2, 3, 4) ($\chi 2$ = 58.76; p = 0.0000; Kendall's Tau b -0.4347 , p = 0.0000).

Since the value of the Kendall's Tau b coefficient was negative at a significance level of p <0.05, among patients with COPD and obesity, patients with a degree of bronchial obstruction GOLD 2 and 3 were significantly more likely than among patients with COPD and normal body weight (31 (35 , 23%) and 50 (56.82%), compared with 17 (19.31%) and 16 (18.18%), respectively). And vice versa - among patients with COPD and normal body weight, patients with a degree of bronchial obstruction GOLD 4 (55 (62.5%) and 7 (7.9%), respectively) were significantly more likely to prevail. There were no patients with the degree of bronchial obstruction GOLD 1 in the study

groups. There were no significant differences between the studied groups 1 and 3 in the distribution of patients with belonging to patient groups A, B, C, D ($\chi 2$ = 1.43; p = 0.2316).

Similar results were obtained when comparing the results of spirometry in groups 1 and 2 (GOLD 1, 2, 3, 4) ($\chi 2$ = 34.26; p = 0.0000; Kendall's Tau b -0.3596, p = 0.0000). Among patients with COPD and overweight, patients with a degree of bronchial obstruction GOLD 2 and 3 were significantly more common than among patients with COPD and normal body weight (32 (36.36%) and 39 (44.31%), compared with 17 (19.31%) and 16 (18.18%), respectively). And, on the contrary, among patients with COPD and normal body weight, patients with a degree of bronchial obstruction GOLD 4 (55 (62.5%) and 17 (19.31%), respectively) were significantly more likely to prevail. There were no patients with the degree of bronchial obstruction GOLD 1 in the study groups. Groups 1 and 2 also significantly differed in the distribution of patients by belonging to patient groups A, B, C, D ($\chi 2$ = 8.123; p = 0.0044; Kendall's Tau b -0.2148, p = 0.0045). Since the value of the Kendall's Tau b coefficient was negative at a significance level of p <0.05, among patients with COPD and overweight, group B patients were significantly more likely to occur than among patients with COPD and normal body weight (16 (18.18%) and 4 (4.54%), respectively). And vice versa - among patients with COPD and normal body weight, group D patients were more common than group 2 (84 (95.45%) and 72 (81.81%), respectively). There were no patients of groups A and C in the studied groups.

We obtained data on a statistically significant higher quality of life in patients with COPD and normal body weight compared to patients with COPD and obesity according to the SF-36 scales, which are defined as the physical component of health (role functioning due to physical condition, which amounted to 35.39 ± 21.59 and 24.24 ± 11.36 points, respectively (F = 5.00, p = 0.0266), the intensity of pain, which was 70.39 ± 39.06 and 56.61 ± 29.31 points, respectively (F = 7.00, p = 0.0089), the general state of health, which was 38.55 ± 11.14 and 34.72 ± 14.32 points, respectively (F = 3.92, p = 0, 04 93)), as well as the psychological component of health (vital activity, which was 43.69 ± 14.94 and 38.23 ± 12.15 points, respectively (F = 7.06, p = 0.0086)).

There were no statistically significant differences in the level of IL-4 between 1, 2 and 3 groups of patients with COPD. As in the level of IL-6 between groups 1 and 3. As for the comparison of groups 1 and 2, the level of IL-6 was significantly higher in the group of patients with COPD and overweight than in patients with COPD and normal body weight 32.36 (8.59; 44.81) and 22 , 31

(4.877; 40.85), respectively (p = 0.0397). Compared to patients with COPD and normal body weight, patients with COPD and obesity had significantly higher levels of TNF-α (0.001 (0.001; 0.3507) and 0.001 (0.001; 0.001) pg / ml, respectively (p = 0.0189)). When comparing the levels of TNF-α in group 1 and 2, the following values were obtained: (0.001 (0.001; 0.5967) and 0.001 (0.001; 0.001) pg / ml, respectively (p = 0.0082).

We found that the level of leptin in patients with COPD and obesity, as well as patients with COPD and overweight compared with patients with COPD and normal body weight, was significantly higher (45.58 ± 29.47 and 13.32 ± 10.81 ng / ml, (F = 92.92, p = 0.0000)), (24.05 ± 19.69 and 13.32 ± 10.81 ng / ml, (F = 20.08, p = 0.0000)) respectively. There were no statistically significant differences in adiponectin level between groups 1 and 3, 1 and 2 (F = 2.41, p = 0.1223), (F = 1.21, p = 0.2726). Also, the resistin level did not have significant differences in groups 1 and 3 (F = 0.01, p = 0.9133), but was significantly lower (7.85 ± 3.90 and 9.54 ± 5.94 ng / ml, respectively (F = 4.94, p = 0.0276) in patients with overweight and COPD to compared with patients with COPD and normal body weight.

THE DISCUSSION OF THE RESULTS:

Thus, reliable relationships between the presence of obesity in asthma patients and the following indicators in the blood serum were revealed: the level of anorexigenic neuropetide Y, which causes insulin resistance - resistin, the level of TNF-α, the indicator of antioxidant activity of the body, and the degree of oxidative damage to biomolecules. As for patients with COPD, a relationship was found between obesity in these patients and the following indicators: levels of IL-6, TNF-α, leptin and resistin.

According to GINA (2019), obesity is a state of mild chronic inflammation with increased pro-inflammatory activity caused by adipocytes. Adipokines are secreted by adipose tissue cells, leptin and adiponectin are some examples of such adipokines, the effect of which on the course of asthma and COPD continues to be studied. Leptin is a pro-inflammatory cytokine and may be one of the factors contributing to an increase in the prevalence of asthma and COPD in obese patients. It stimulates the release of NO, IL-6 and IL-8 and TNF-α. (9) There are already studies in which it was proven that the experimental administration of

TNF-α to mice increased leptin levels. (10) Higher leptin levels are recorded in patients with asthma; this is more clearly seen in women than in men, and more pronounced in premenopausal women than in postmenopausal women. In turn, adiponectin plays the opposite role, inhibiting inflammation.

Our study also showed that adiponectin acts as an inhibitor of inflammation in asthma, since it has a positive correlation with spirometry parameters. Data on the relationship between asthma and adiponectin are contradictory. Some studies suggest that low adiponectin levels are more likely to cause asthma in women (11), while others generally deny any correlation. (12) Other studies report that higher adiponectin levels correlate with mild asthma, but only in women, while in men, this relationship is the opposite: asthma, which requires more active drug support, has been associated with higher adiponectin. (13) A study was also conducted that analysed serum adiponectin levels and adiponectin mRNA expression in abdominal adipose tissue in obese patients. Obese and asthma patients had lower
adiponectin mRNA expression than obese patients without asthma, but serum adiponectin levels did not differ significantly in these groups. (14) There is also information about a decrease in serum adiponectin, but only during exacerbations in asthma patients. These data suggest that a decrease in adiponectin may not be a predictor, but a consequence of the clinical course of asthma.

Oxidative stress plays an important role in the pathogenesis of asthma. According to recent studies, biomarkers of oxidative stress are higher in obese patients and correlate with BMI (15), while biomarkers of antioxidant defense are inversely correlated. In our study, we observed the same relationship in patients with asthma with different body weights. As for information on neuropeptide Y, the available scientific data on the relationship between neuropeptide Y and asthma are ambiguous. Several studies have reported that certain genotypes of neuropeptide Y are associated with asthma. (16) Y1 receptors of neuropeptide Y play an important role in allergic inflammation of respiratory airways. One study also reports that during exacerbations of asthma, neuropeptide Y levels increase. In our study, neuropeptide Y levels were significantly higher in obese and overweight patients with asthma and had an inverse correlation with spirometry parameters, which indicates a negative effect on the clinical course of asthma. Therefore, it can be said that the severity of the clinical course of asthma in obese patients is associated with various factors, including oxidative stress and levels of leptin, adiponectin, and neuropeptide Y. Although the exact mechanisms remain unclear.

Conclusion: the data obtained allow us to conclude that obesity as a source of chronic systemic inflammation is a predictor of the adverse course of asthma and COPD. To numerically determine the effect of obesity on these pulmonological pathologies, the following serum indices can be used: leptin, resistin, TNF-α. In addition, for asthma, in particular, neuropetid Y, the total oxidative damage and the total antioxidant status are promising markers.

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