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CLINICAL AND METABOLIC FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN COMBINATION WITH OBESITY

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Abstract:

Background. *According to recent studies, the prevalence of obesity in patients with chronic obstructive pulmonary disease (COPD) is up to 50%. Several studies have reported more pronounced respiratory symptoms, a greater frequency of exacerbations, a more pronounced limitation in daily activities in patients with COPD and obesity. However, other studies decribed "obesity paradox" with a favorable prognosis of COPD in obese patients.*

Objective: *to evaluate the features of the disease course, the severity of clinical manifestations, including symptoms, comorbidities and lung function, as well as the characteristics of the cytokine profile in patients with COPD and obesity.*

Material and methods. *The study included 192 patients with COPD (GOLD 2-4, group D). The first group included 96 patients with COPD with normal body weight: 71 men and 25 women, mean age 62.20 ± 8.13 years. The second group - 96 patients with COPD and obesity: 64 men and 24 women, mean age 62.14 ± 5.26 years. In all patients the frequency of COPD exacerbations in the last 12 months and the severity of symptoms were assessed. Spirometry, six-minute walking test were performed. BODE index was counted. The cytokine profile and the level of adipokines were evaluated.*

Results. *Patients with COPD and obesity were characterized by low severity of symptoms (dyspnea, sputum production, weakness) with relatively high values of FEV1, FVC, relatively low risk of COPD exacerbations, and low BODE index, with frequent combination with diabetes, arterial hypertension, the greater severity of systemic inflammation, in particular significant differences in the levels of CRP, interferon-γ, TNF-α, TNF-R1, TNF-R2.*

Conclusion. *It seems appropriate to single out individual phenotypes of COPD with normal body weight and obesity to identify new approaches and strategies to therapy.*

Key words: *chronic obstructive pulmonary disease, obesity, spirometry, interleukins, BODE index.*

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INTRODUCTION:

Over the past years chronic obstructive pulmonary disease (COPD) has been the fourth most common cause of death worldwide, and is projected to move to third place by the year 2020 [1-3]. According to a large epidemiological study conducted in 2012, the annual mortality from COPD exceeded 3 million people, which accounted for about 6% of all deaths worldwide [4].

According to various studies, the prevalence of obesity in patients with COPD ranges from 10% to 50%. The relationship between obesity and the incidence of COPD was also shown [5]. However, it is unclear whether obesity has a detrimental effect on the course of COPD. Low body mass index (BMI) was regarded as an independent risk factor for death in patients with COPD [6]. Several studies have reported more pronounced respiratory symptoms, a greater frequency of exacerbations, a more pronounced limitation in daily activities, and a deterioration in the quality of life in patients with COPD and obesity [7]. However, the results are rather contradictory. In addition, the pharmacological and non-pharmacological treatment of COPD can hide the effects of comorbidities, including obesity, and this factor has not been taken into account in almost any large study.

Increased expression and secretion of pro-inflammatory adipokines as a result of obesity and/or hypoxia in patients with COPD, may be a mechanism that aggravates the general systemic nature of inflammation in this multicomponent disease. Despite the available results of experimental work on animals with the identification of the effects of hypoxia in adipocyte cell cultures, as well as data from a few clinical studies, the extent to which adipose tissue production and release of inflammatory cytokines contributes to chronic systemic inflammatory syndrome in COPD is not sufficiently defined and requires further investigation.

The aim of this study was to evaluate the features of the disease course, the severity of clinical manifestations, including symptoms, comorbidities and lung function, as well as the characteristics of the cytokine profile and adipokine level in patients with COPD and obesity.

MATERIAL AND METHODS:

The study included 192 patients with COPD (GOLD 2-4, group D). The diagnosis of COPD was established in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD 2019), on the basis of an assessment of symptoms, history, objective status, spirometry (in standard mode with salbutamol 400 μg) [8]. The total number of patients was determined by the sum of patients from the two groups. The first group (group 1) included 96 patients with COPD with normal body weight: 71 (73.96%) men and 25 (26.04%) women aged 43 to 72 years (mean age 62.20 ± 8.13 years). The second group (group 2) - 96 patients with COPD and obesity: 64 (66.67%) men and 24 (25.0%) women aged 50 to 72 years (mean age 62.14 ± 5.26 years). The presence of normal body weight or obesity was established in accordance with anthropometric data - according to the level of body mass index (BMI): 18.5-24.99 kg / m^2 - normal body weight, 30 kg / m^2 and more - obesity.

The exclusion criteria were: 1) patient participation in any interventional study, 2) COPD exacerbation, 3) concomitant lung diseases, such as confirmed or suspected malignant lung disease or other respiratory disease, such as interstitial pulmonary fibrosis, tuberculosis, sarcoidosis, bronchial asthma, bronchiectasis, 4) concomitant diseases of other organs and systems, such as acute cardiovascular diseases, chronic kidney diseases and liver failure.

All patients gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Voronezh State Medical University (protocol no. 1 from February 21, 2018).

Standard treatment for COPD included a long-acting anticholinergic drug or a long-acting β2-agonist in combination with a long-acting anticholinergic drug or a long-acting β2 agonist in combination with an inhaled corticosteroid. Patients used short-acting β2-agonists on demand.

The clinical course of COPD was assessed by the frequency of exacerbations in the last 12 months that did not require hospitalization, and the frequency of hospitalizations for exacerbations of COPD in the last 12 months.

Among concomitant diseases, the presence of coronary artery disease (CAD), arterial hypertension (AH), chronic heart failure (CHF), and diabetes mellitus (DM) was evaluated.

To assess the severity of cough, sputum production, shortness of breath, and general weakness, a visual analogue scale (VAS) was used - from 0 to 10 cm, where 0 is the absence of a symptom, 10 is the

maximum severity of the symptom. The mMRC scale (modified by the Medical Research Council) was used to assess dyspnea. The severity of symptoms of COPD and the effect of the disease on the daily activities of patients were assessed using the COPD Assessment Test (CAT) [9].

The post-bronchodilation values of FEV1, FVC, FEV1/ FVC were assessed by spirometry.

To assess the exercise tolerance the six-minute walk test (6MWT) was used [10].

The BODE index was calculated according to the generally accepted method, taking into account FEV1, mMRC, 6MWT, BMI [11].

To assess the features of cytokine profile in patients with COPD and obesity compared with patients with COPD and normal body weight, a biochemical analysis of venous blood was performed. The levels of interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4), interleukin-10 (IL-10), as well as the levels of interferon-gamma, soluble receptors for tumor necrosis factor alpha type 1 and 2 (TNF-R1, TNF-R2) were evaluated using enzyme-linked immunosorbent assay (ELISA). In addition, the serum concentration of highly sensitive C-reactive protein (CRP) was evaluated.

Statistical processing was performed using the STATGRAPHICS 5.1 Plus for Windows software package. The normal distribution of data in the samples was evaluated using the Kolmogorov test. Quantitative data (with a normal distribution) are presented in the form M ± σ, where M is the sample mean, σ is the standard deviation. In the absence of a normal distribution in the samples, the data are presented as a median and upper and lower quartiles. Qualitative variables were compared using the $\chi 2$ test or the Fisher exact test. Comparison of quantitative data was performed using one-way analysis of variance (ANOVA) or Mann-Whitney U-test. Differences were considered statistically significant at a significance level of $p < 0$.

RESULTS:

According to the results of a comparative analysis, the frequency of COPD exacerbations for the previous year, that did not require hospitalization, was significantly higher in patients with COPD and normal body weight than in patients with COPD and obesity: 1.21 ± 0.83 and 0.96 ± 0.42 respectively (p = 0.016). The frequency of exacerbations of COPD for the previous year that required hospitalization, in patients with COPD with normal body weight was also significantly higher than in patients with COPD and obesity: 1.82 ± 0.94 and 1.5 ± 0.81, respectively (p = 0.0145).

In patients with COPD and obesity the severity of dyspnea, sputum production and weakness were significantly lower compared with patients with COPD with normal body weight. The indicated spirometry parameters in patients with COPD and obesity were significantly higher than in patients with COPD with normal body weight.

The distance covered in 6MWT was less in patients with COPD with normal body weight compared with patients with COPD and obesity: 251.58 ± 183.54 m and 293.34 ± 124.89 m, respectively (p = 0.0794).

The average BODE index in patients with COPD and normal body weight was significantly higher than in patients with COPD with obesity: 6.23 ± 2.81 and 4.53 ± 2.11, respectively (p = 0.0000).

In patients with COPD and obesity compared with patients with COPD with normal body weight, the levels of CRP, interferon-γ, TNF-α, TNF-R1, TNF-R2 were significantly higher. At the same time, the values of IL-4, IL-6, IL-8, IL-10 in patients with the studied groups did not differ significantly.

The results of our study revealed significant differences in the estimated indicators between patients with COPD and normal body weight and patients with COPD and obesity. In particular, in patients with COPD and normal body weight compared with patients with COPD and obesity there were significantly more frequent exacerbations of COPD, both with hospitalization and not requiring hospitalization. These data indicate that a high BMI is a predictor of favorable outcome in terms of the frequency of COPD exacerbations. However, the impact of overweight and obesity on the outcome of COPD has not been fully clarified. Cao et al. conducted a meta-analysis of 22 studies with 21,150 participants and concluded that the presence of overweight and obesity in patients with COPD was associated with a lower risk of death (RR 0.47 (95% CI 0.33–0, 68) and 0.59 (95% CI, 0.38–0.91), respectively), compared with patients with normal BMI [12]. On the other hand, a multicenter prospective cohort study conducted by Lambert et al. showed that obesity was associated with worse outcomes of COPD, including severe exacerbations, as well as more severe dyspnea (according to mMRC) during 6MWT [13].

Our study revealed a greater severity of systemic inflammation in patients with COPD and obesity. Even in patients with stable COPD, an increased level of inflammatory proteins in the systemic circulation, including C-reactive protein, TNF-α, IL-6 and IL-8, has been described [14]. A small but significant increase in the levels of circulating soluble TNF-55 and TNF-75 receptors (sTNF-R55 and sTNF-R75), IL-10 and IL-18 were also reported in patients with COPD [15, 16]. It is important to note that a number of studies have shown a link between the level of inflammatory markers, in particular CRP and IL-6, in the bloodstream and a decrease in FEV1 [17]. Moreover, some evidence suggests that systemic inflammation is probably not balanced by activation of anti-inflammatory factors. Dentener et al. showed that the levels of soluble receptor II of anti-inflammatory interleukin-1 (sIL-1RII) were similar in patients with stable COPD and in healthy individuals, despite a significantly increased level of sTNF-R55 in the first [18].

Regarding the comparative assessment of the severity of symptoms with the use of assessment scales and questionnaires, we found that in patients with COPD and obesity, the severity of dyspnea, sputum production and general weakness were significantly lower compared to patients with COPD with normal body mass, indicating a more favorable course of the disease in patients with COPD and obesity compared with patients with COPD and normal body weight in terms of the subjective perception of the symptoms by the patients themselves. Thus, the obesity paradox in relation to COPD is expanding and includes not only a lower frequency of exacerbations and hospitalizations for exacerbations of COPD, but also less pronounced symptoms, in particular shortness of breath, sputum production, and general weakness. At the same time, the severity of cough, the total score on the CAT questionnaire was not significantly different. This could possibly be related to a more extended assessment of the subjective perception of not only the specific symptoms of the disease, but also certain aspects of the life of patients with COPD, assessed using the specified questionnaire.

In our study, the estimated parameters of respiratory function (FEV1, FVC, FEV1/ FVC) in patients with COPD and obesity were significantly higher than in patients with COPD with normal body weight. Similar results were also obtained in other studies [19]. However contradictory data exists and it indicates the need for a more detailed study of this issue using body plethysmography and other methods for assessing respiratory function and lung volumes.

We draw attention to the result of a comparative assessment of the BODE index, which summarizes the data of spirometry, the severity of dyspnea, 6MWT, BMI, and is of great predictive value in relation to the survival of patients with COPD. The higher the BODE index, the worse the survival rate. According to our results the BODE index value in patients with COPD and normal body weight was significantly higher than in patients with COPD with obesity.

CONCLUSION:

Taking into account the obtained results, it seems appropriate to single out individual phenotypes of COPD with normal body weight and obesity. Patients with COPD and obesity are characterized by low severity of symptoms (shortness of breath, sputum production, general weakness) with relatively high values of FEV1, FVC, relatively low risk of exacerbations of COPD and hospitalizations, and a low BODE index, with frequent combination with diabetes, AH, which is possible reflects a high cardiometabolic risk in these patients. In addition, in patients with COPD and obesity, unlike patients with COPD with normal body weight, the severity of systemic inflammation is significantly higher, in particular, based on statistically significant differences in the levels of CRP, interferon-γ, TNF-α, TNF-R1, TNF-R2. However, this trend did not extend to the classical representatives of the cytokine profile - IL-4, IL-6, IL-8, IL-10, that can be explained by more complex mechanisms which require further study. Further in-depth studies in this area may allow to identify new approaches to anti-inflammatory therapy in patients with COPD and obesity, develop new drugs, expand the indications for use of already available drugs, for example, inhaled corticosteroids, roflumilast.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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