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BODY TISSUE TYPE COMPOSITION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND OBESITY

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Abstract:

Background. *Chronic obstructive pulmonary disease (COPD) is one of the most widespread diseases worldwide. Evaluation of body composition and nutrition is currently considered to be an important factor in diagnosis, assessment and treatment of COPD.*

Objective: *to describe body composition in COPD patients (in accordance with body weight) and to analyze association between body composition and disease severity (symptoms, spirometry, and systemic inflammation markers).*

Material and methods. *The study included 176 patients with COPD, which were divided into 2 groups. The first group included 88 normal weight patients with COPD: 71 men and 17 women, mean age 62.40 ± 8.83 years. The second group included 88 patients with COPD and obesity: 64 men and 24 women, mean age 62.94 ± 5.96 years. We assessed the severity of symptoms such as dyspnea, sputum production, fatigue. Spirometry, six-minute walk test and analysis of body tissue type composition were performed. Levels of leptin, adiponectin, interleukins-4,6,8,10, interferon-γ, c-reactive protein (CRP), tumor necrosis factor receptor 1 (TNF-R1), tumor necrosis factor receptor 2 (TNF-R2), tumor necrosis factor alpha (TNF-α) were measured in blood serum.*

Results. *In patients with COPD and obesity, a low severity of symptoms (specifically dyspnea, sputum production and fatigue) was observed. Levels of CRP, interferon-γ, TNF-α, TNF-R1, TNF-R2 were significantly higher in obese patients compared with normal weight patients, indicating greater systemic inflammation. Patients with COPD and obesity were significantly higher in % fat while normal weight patients were significantly higher in % water. Waist, hip circumference and their ratio were also significantly higher in patients with COPD and obesity. There was no difference in % of muscle mass.*

Conclusion. *It is necessary to distinguish COPD phenotypes, such as COPD phenotype with normal weight and COPD phenotype with obesity to identify new possible approaches to its assessment and treatment. Further investigations of body tissue type composition are required to determine its role in COPD pathophysiology.*

Key words: *chronic obstructive pulmonary disease, obesity, body composition, interleukins, fat*

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INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is one of the most widespread diseases worldwide. The prevalence of COPD, its morbidity and mortality vary both among countries and among population groups within countries. Based on the results obtained in the BOLD program (Burden of Obstructive Lung Diseases), as well as in other epidemiological studies, the number of reported cases of COPD in 2010 was 384 million, with a total prevalence of this disease worldwide of 11.7% (95% CI 8.4-15%) [1].

Patients with COPD often have comorbidities, such as cardiovascular disease or lung cancer, for which smoking is also a risk factor. Other pathological conditions, such as anxiety, depression, osteoporosis, anemia, diabetes mellitus (DM), metabolic syndrome and obesity, are also often associated with COPD [2-6]. This comorbid pathology affects the health of COPD patients and the outcome of the disease [7, 8].

In the recent years a lot of attention is paid to the topic of nutrition in COPD patients [9]. Evaluation of body composition and nutrition is currently considered to be an important factor in diagnosis, assessment and treatment of COPD. Prevalence of fat component and deficiency of lean body mass is often found in overweight patients with COPD [1]. Trophological insufficiency is an unfavorable factor in predicting the course of chronic diseases, leading to the progression of cardiovascular pathology [10]. Currently, in addition to anthropometry and general clinical indicators of lipid, carbohydrate and protein metabolism, there are modern methods for assessing the nutritional status of patients, which include bioimpedansomerism [11], determination of the level of serum adipokines [12].

The aim of the study: to describe body composition in COPD patients (in accordance with body weight) and to analyze association between body composition and disease severity (symptoms, spirometry, systemic inflammation markers)

MATERIALS AND METHODS:

The study included 192 patients with COPD (GOLD 2-4, group D). The first group (group 1) included 88 patients with COPD with normal body weight: 71 (80.68%) men and 17 (19.32%) women aged 43 to 72 years (mean age 62.40 ± 8.83 years). The second group (group 2) - 88 patients with COPD and obesity: 64 (72.73%) men and 24 (27.27%) women aged 50 to 72 years (mean age 62.94 ± 5.96 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).

All patients received standard treatment for COPD.
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) [13].

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 [14].

The analysis of body composition was performed using bioelectric impedance (BC-555 fat mass analyzer, Tanita Corporation, Japan). The percentage of visceral fat, water, muscle and bone mass were estimated.

To assess the features of cytokine profile, as well as the level of adipokines, 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). The levels of adipokines - leptin, adiponectin - were also determined using 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:

Comparative characteristics of patients in group 1 (COPD and normal body weight) and group 2 (COPD and obesity) are presented in Table 1.

Table 1. Characteristics of patients in the studied groups.

Parameters	Group 1 (n = 88)	Group 2 (n = 88)
Women, n (%)	17 (19.3)	24 (27.3)
Men, n (%)	71 (80.7)	64 (72.7)
Age, years (M ± σ)	62.40 ± 8.83	62.94 ± 5.96
Smoking history, packs-years (M ± σ)	31.3 ± 15.7	28.9 ± 16.1
Exacerbation history, events/year (M ± σ)	3.03 ± 2.77	2.46 ± 1.23
Patients using long-acting anticholinergic drugs, n (%)	52 (59,1)	44 (50)
Patients using long-acting β2-agonists, n (%)	88 (100)	84 (95.5)
Patients using short-acting β2-agonists, n (%)	84 (95.5)	80 (90.9)
Patients using inhaled corticosteroids, n (%)	36 (40.9)	40 (45.5)

Groups 1 and 2 were significantly different in % fat (higher in patients with COPD and obesity) and % water (higher in patients with COPD and normal body weight). Waist, hip circumference and their ratio were also significantly higher in patients with COPD and obesity.

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 (7.14±2.32 and 8.60±1.44 (p=0.0000); 3.97±1.86 and 4.82±2.75 (p = 0.0170); 6.66±2.06 and 7.70±2.65 (p = 0.0040), respectively). Such spirometry parameters as FEV1, FVC and FEV1/FVC in patients with COPD and obesity were significantly higher than in patients with COPD with normal body weight (47.44±15.30 and 32.44±16.24 (p = 0.0000); 74.72±19.78 and 55.40±21.45 (p = 0.0000); 63.09±8.19 and 56.65±8.94 (p = 0.0000), respectively).

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 (p = 0.0021, p = 0.0029, p = 0.0189, p = 0.0108, p = 0.0000, respectively). 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 (p = 0.5123, p = 0.1096, p = 0.1575, p = 0.7197, respectively).

In patients with COPD and obesity compared with patients with COPD with a normal body weight, serum leptin levels were significantly higher. Adiponectin values, on the contrary, prevailed in patients with normal body weight, but this difference was not statistically significant (p = 0.1223).

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. 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 [15]. 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 [16, 17]. 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 [18]. 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 [19].

According to several studies patients with COPD and obesity had lower FVC values than patients with COPD with normal body weight [20, 21]. However, 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 [22].

It is well known that in most obese people, serum leptin levels are higher and adiponectin is lower than in non-obese people, indicating chronic inflammation in obese patients [23]. Krommidas et al. reported a higher leptin / adiponectin ratio in exacerbations of COPD and a lower ratio in the absence of exacerbation [24]. However, the relationship between adipokine levels and COPD remains controversial. Wolk et al. showed that a low BMI with a high leptin / adiponectin ratio and a high BMI with a low leptin / adiponectin ratio were similarly associated with better cardiovascular outcomes, indicating the complexity of pathophysiology [25]. The results of studies involving patients with COPD and obesity, combined with the knowledge about the pleiotropic effects of most inflammatory mediators, suggest that there may be physiological and clinical cross-links between the lungs and adipose tissue. First, the receptors for two typical adipokines, leptin and adiponectin, are expressed in peripheral tissues, including the lungs. Interestingly, the increased expression of leptin in the bronchial mucosa is observed in patients with COPD and is associated with inflammation and airway obstruction [26]. In addition, leptin receptor polymorphism is associated with a decrease in pulmonary function in patients with COPD, while adiponectin can weaken allergen-induced airway inflammation and hypersensitivity that may determine its potential protective role in the airways [27].

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. Obesity was associated with more favorable prognosis in patients with COPD, while suffering from various chronic diseases, including cardiovascular diseases. Similar data were obtained in some other studies and were called obesity paradox [28]. The mechanism of this phenomenon is still unclear. A possible answer to this question can be the significant differences shown by us in the body composition of patients with COPD with normal body weight or obesity, in particular, significant predominance of % fat in patients with obesity and % water in patients with normal body weight, as well as the distribution of adipose tissue in the form of a significant prevalence of the waist/hips ratio in patients with obesity, meeting the criteria for a metabolically unhealthy phenotype [29]. It is extremely important that there is no difference in % of muscle mass, which is actively discussed and often used as a possible factor explaining the described differences in clinical manifestations, spirometry, and even clinical outcomes, including mortality.

CONCLUSION:

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. 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. A significant predominance of % fat in patients with obesity and % water in patients with normal body weight was found while there was no difference in % of muscle mass, which requires further investigations of body tissue type composition and its role in COPD pathophysiology.

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

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