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The intensity of oxidative stress and systemic inflammation in patients with a combination of bronchial asthma and chronic obstructive pulmonary disease

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Abstract

Background. Chronic obstructive pulmonary disease and bronchial asthma, when combined in one patient, are characterized by a low level of control. Excess weight aggravates the course of obstructive diseases. The study of the features of this syntropy will improve the effectiveness of therapeutic measures.

Aim. The study of the level of cytokines and carbonylated proteins in patients with a combination of bronchial asthma and chronic obstructive pulmonary disease with overweight and normal weight during an exacerbation.

Material and methods. The study included 136 people: the first group — a combination of bronchial asthma and chronic obstructive pulmonary disease (n=30), the second — bronchial asthma (n=36), the third — chronic obstructive pulmonary disease (n=29), the fourth — volunteers without respiratory diseases (n=41). Each group was divided into two subgroups depending on the body mass index (less than 25 kg/m² or 25 kg/m² and more). The concentrations of interleukins-6 and -8, tumor necrosis factor α in blood plasma were determined by enzyme immunoassay. The level of carbonylated plasma proteins was assessed spectrophotometrically. Statistical processing was performed in the Statistica 10.0 program using nonparametric criteria. The correlation of the studied parameters was assessed using the Spearman coefficient.

Results. In patients with a combination of bronchial asthma and chronic obstructive pulmonary disease, statistically significant positive correlations between the levels of interleukins-6 and -8, tumor necrosis factor α and carbonylated proteins were found — 0.51, 0.59 and 0.55, respectively ($p < 0.05$). Patients of the first group with overweight differed by 37.5% in higher levels of interleukin-6 compared with patients with body mass index < 25 kg/m².

Conclusion. The intensity of systemic inflammation in patients with a combination of bronchial asthma and chronic obstructive pulmonary disease during exacerbation correlates with the intensity of oxidative damage.

Keywords: bronchial asthma, COPD, overweight, cytokines, carbonylated proteins.

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List of abbreviations

BA — bronchial asthma; IL — interleukin; BMI — body mass index; OMP — oxidatively modified proteins; OS — oxidative stress; SPOM — spontaneous protein oxidative modification; TNF α — tumor necrosis factor α ; COPD — chronic obstructive pulmonary disease; ACO — asthma–COPD overlap

Background

The term “asthma–COPD overlap” (ACO) refers to the coexistence of bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) in the same patient. The pathophysiological mechanisms of ACO are not yet fully understood, and its early detection in patients has not yet been achieved, leaving them without appropriate therapy for an extended period [1].

The estimation of ACO prevalence varies depending on the criteria used. However, cohort stu-

dies indicate that the combination of BA and COPD in a patient occurs in 20% to 30% of all patients with chronic respiratory diseases accompanied by obstructive syndrome [1, 2].

In recent years, studies have reported the modifying effect of excess adipose tissue on the intensity of generalized inflammation in COPD and BA [3–5]. Obesity significantly affects the pathogenesis of BA, changing the type of inflammation from Th2 to Th1 and Th17, which leads to the low efficacy of inhaled glucocorticoids and an uncontrolled

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course of the disease [6]. Excess adipose tissue can impair external respiratory function and decrease lung diffusion capacity [5]. However, the paradox of obesity in COPD patients is well known. Peltola et al. reported that the survival rate of overweight patients with ACO is comparable to that of overweight patients with COPD [7].

Currently, the most widely available biomarkers of the inflammatory response include routine research methods, such as determining the levels of C-reactive protein, fibrinogen, and blood eosinophils or the ratio of cellular elements in the general blood count. Moreover, specific indicators reflecting the Th2-type immune response, such as the content of NO(II) in exhaled air and the level of immunoglobulin E in the blood, are considered [8]. Other potential biomarkers evaluated frequently include cytokines that specifically mediate the type of immune response and the participation of different cell types in the inflammatory response, such as interleukins (i.e., IL-6 and IL-8) and tumor necrosis factor α (TNF α) [9].

Tobacco-smoke-induced oxidative stress (OS) hinders inhaled glucocorticoid therapy [10]. Impaired redox regulation in immune system cells contributes to the persistence of chronic inflammation associated with OS [11]. Several studies have shown a correlation between the intensity of local and systemic inflammation in BA and COPD and the level of OS markers in cells and blood plasma [12, 13]. Currently, studies of the changes in the level of OS markers in patients with ACO are lacking.

Among the possible biomarkers of OS, the most promising are carbonylated proteins found in blood plasma. These proteins are readily available for study in routine practice [13, 14]. Carbonylated proteins are formed as a result of oxidative modification and are characterized by greater stability in biological media than lipid peroxidation products. These proteins are direct markers of damage and can reflect the intensity of OS associated with inflammation and hypoxia [14].

Thus, the widespread phenomenon of ACO, the need to search for new biomarkers, and the lack of data on the severity of OS in patients with ACO indicate the expediency of investigating the relationship between OS and systemic inflammation in this category of patients. The different nature of the modifying effect of excess body weight on inflammation in COPD and BA makes it interesting to evaluate the effect of excess body weight on both systemic inflammation parameters and OS markers in patients with ACO.

This study aimed to investigate the levels of cytokines and carbonylated proteins in overweight

and normal-weight patients with combined BA and COPD during exacerbation.

Materials and methods

This study was approved by the local ethical committee of Pavlov Ryazan State Medical University (Protocol No. 12, dated May 25, 2021).

This study recruited 136 participants, including healthy volunteers and patients receiving treatment at the Regional Clinical Hospital and City Clinical Polyclinic No. 6 in Ryazan, from May 28, 2021 to August 6, 2021. This study was a pilot study. The minimum sample size ($n = 28$) was calculated based on a statistical power of 80% and a significance level of 0.05, which were determined based on the minimum clinical significance of the change in the level of oxidatively modified proteins (OMP) in the cell suspension of mononuclear leukocytes in patients with COPD. This significance was established based on the results of a previous study [13–15].

Four groups were formed for the study: Group 1 consisted of patients with a combination of BA and COPD (ACO; $n = 30$); Group 2 consisted of patients with BA ($n = 36$); Group 3 consisted of patients with COPD ($n = 29$); and Group 4 consisted of volunteers without respiratory diseases ($n = 41$), serving as the control group. Each group was further divided into subgroups based on their body mass index (BMI), with subgroups having a BMI < 25 kg/m² and BMI ≥ 25 kg/m².

This study included participants who provided signed informed consent and met specific inclusion criteria. For COPD patients, these criteria included being between the ages of 40 and 70 years, having a baseline post-bronchodilation modified Tiffno index of 0.7 or less, and experiencing an exacerbation period. For patients with BA and ACO, the inclusion criteria were being between the ages of 40 and 70 years, having a confirmed diagnosis of BA or ACO according to the Global Strategy for the Treatment and Prevention of BA (2021), and experiencing an exacerbation period. The inclusion criteria for the group of volunteers without respiratory diseases were individuals between the ages of 40 and 70 years and the absence of any documented chronic lung disease in their medical history.

The exclusion criteria for all groups included age below 40 years or above 70 years, ≤ 18 kg/m², BMI ≥ 40 kg/m², pharmacotherapy with systemic glucocorticoids before the study, secondary obesity, respiratory pathology other than COPD, BA, and ACO, cardiovascular pathology with chronic heart failure stage IIA or higher, diabetes mellitus, other concomitant chronic diseases and their complications, alcoholism, and drug addiction.

Table 1. Clinical characteristics of the study groups

Index	ACO, <i>n</i> = 30 (Group 1)	BA, <i>n</i> = 36 (Group 2)	COPD, <i>n</i> = 29 (Group 3)	Healthy volunteers, <i>n</i> = 41 (Group 4)
Age, years	64,5 [57,25; 65] $p_{1-2}=0,34874$ $p_{1-3}=1$ $p_{1-4}=1$	58 [49; 63,25] $p_{2-3}=0,13999$ $p_{2-4}=0,34874$	65 [63; 65] $p_{3-4}=1$	59 [57; 65]
BMI <25 kg/m ² BMI ≥25 kg/m ²	13 17	12 24	19 10	11 30
Age by BMI, years: <25 kg/m ² ≥25 kg/m ²	59 [57; 60] 60 [58; 65,25] $p=0,3025$	55 [44,25; 62,25] 60,5 [49,0; 64,0] $p=0,4079$	65 [62; 65] 65 [63,5; 65] $p=0,5122$	58 [56; 64] 60,5 [59,0; 65,75] $p=0,2828$
Obesity I Obesity II Obesity III	6 2 0	3 8 0	2 2 0	11 3 0
Gender: Male Female	26 4	8 28	29 0	9 32
Smoking: Smokers Ex-smokers Nonsmokers	16 14 0	3 0 33	22 7 0	2 0 39
FEV ₁ , %	43 [36; 57] $p_{1-2}<0,0001$ $p_{1-3}=0,2678$ $p_{1-4}<0,0001$	83,5 [68; 90,5] $p_{2-3}<0,0001$ $p_{2-4}=0,0046$	39 [32; 47] $p_{3-4}<0,0001$	92 [89; 96]
FEV ₁ by BMI, %: <25 kg/m ² ≥25 kg/m ²	43 [34; 59,5] 48 [37; 61] $p=0,4253$	85 [52,75; 91,25] 82 [66; 92,25] $p=0,9538$	37 [32; 44] 39,5 [36; 64,5] $p=0,2407$	95 [89; 98] 92 [88; 94,25] $p=0,1242$
SpO ₂ , %	93 [89; 94] $p_{1-2}<0,0001$ $p_{1-3}=0,7613$ $p_{1-4}<0,0001$	97 [97; 98] $p_{2-3}<0,0001$ $p_{2-4}>0,9999$	91 [84; 93] $p_{3-4}<0,0001$	98 [97; 98]
SpO ₂ by BMI, %: <25 kg/m ² ≥25 kg/m ²	92 [89; 94] 93 [91; 96] $p=0,3185$	98 [97; 98] 97 [97; 98] $p=0,1147$	91 [86; 94] 87 [83,75; 91,5] $p=0,1444$	98 [97; 99] 98 [97; 98] $p=0,2461$

Note: ACO, asthma–COPD overlap; BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV₁, forced expiratory volume in the first second; SpO₂, blood oxygen saturation.

The criteria used to exclude the infectious nature of exacerbation in the COPD, BA, and ACO groups were as follows:

1. Body temperature elevation above 37°C during the month preceding the study;
2. Presence of green or yellow-green sputum (if applicable);
3. History of the disease (provoking factors, such as hypothermia, stress, and contact with people who have symptoms of acute respiratory viral infection);
4. Level of high-sensitivity C-reactive protein (>5 mg/L);
5. Antibiotic therapy during the month preceding the study.

The clinical characteristics of the patients are listed in Table 1.

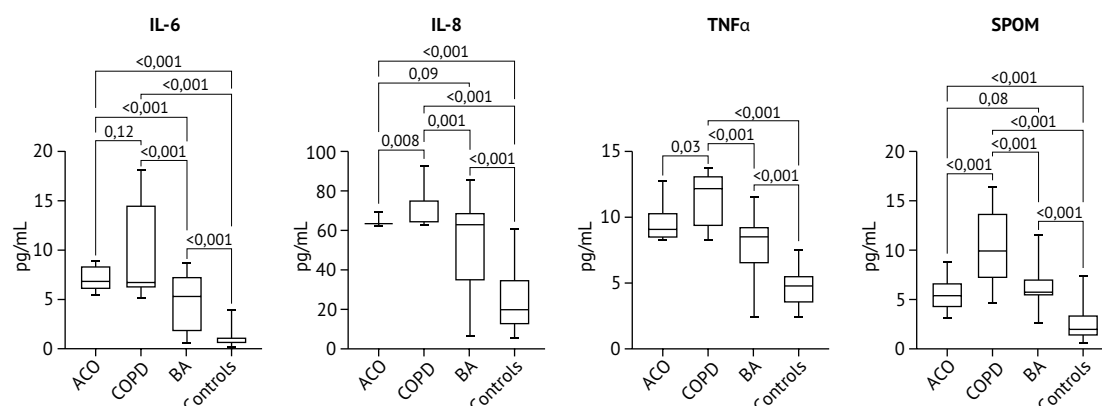
The groups under study were comparable in terms of age, as shown in Table 1.

Males were predominant in the ACO and COPD groups, whereas females were predominant among the healthy respondents and in the BA group. Patients with COPD and ACO showed statistically significant differences from the control and BA groups in forced expiratory volume in the first second and blood oxygen saturation, as indicated in Table 1. The study subgroups, categorized by BMI, were statistically similar in terms of age, external respiratory function, and blood oxygen saturation (Table 1).

Table 2. Correlations between the concentrations of IL-6, IL-8, and TNF α and the levels of carbonylated proteins in blood plasma in the study groups

Patient groups	n	IL-6 and SPOM		IL-8 and SPOM		TNF α and SPOM	
		rs	p	rs	p	rs	p
ACO	30	0,51	0,0038	0,59	0,00061	0,55	0,002
BA	36	0,53	0,000818	0,43	0,0091	0,68	<0,001
COPD	29	0,76	0,000002	0,67	0,000071	0,30	0,108
Controls	41	−0,04	0,805	−0,02	0,909	0,13	0,435

Note: IL, interleukin; TNF α , tumor necrosis factor α ; SPOM, spontaneous protein oxidative modification; ACO, asthma–COPD overlap; BA, bronchial asthma; COPD, chronic obstructive pulmonary disease.

**Fig. 1.** Indicators of systemic inflammation and oxidative stress (OS) in the study groups. The p values are given above the figures. IL, interleukin; TNF α , tumor necrosis factor α ; SPOM, spontaneous protein oxidative modification; ACO, asthma–COPD overlap (Group 1, n = 30); COPD, chronic obstructive pulmonary disease (Group 3, n = 29); BA, bronchial asthma (Group 2, n = 36); Group 4 (n = 41), volunteers without respiratory diseases.

At the time of inclusion in the study, the patients received the following therapy:

1. COPD (n = 29): two doses of metered aerosol inhaler with fenoterol + ipratropium bromide 20/50 mcg three times a day.

2. BA (n = 36): 32 patients received beclometasone 250 mcg twice daily and ipratropium bromide + fenoterol (Berodual H) two doses three times daily and 4 patients received budesonide + formoterol (Foradil Combi) 12/400 mcg twice daily.

3. ACO (n = 30): beclometasone 250 mcg twice daily and bromide + fenoterol (Berodual H) two doses three times daily.

All study participants underwent a general clinical examination, which included history taking, examination, and evaluation of external respiratory function using a MicroLab spirometer and pulse oximetry.

BMI was calculated using the following formula:

$$\text{BMI} = \text{body weight/height}^2 \text{ (kg/m}^2\text{)}.$$

Blood samples were taken before treatment, and the concentrations of IL-6, IL-8, and TNF α in blood plasma were determined using the HUMAN IL-8/NAP-1, HUMAN IL-6, HUMAN TNF alpha,

and hsCRP Platinum ELISA kits (Affymetrix eBioscience Inc., Vienna, Austria) and analyzed using the Immunoenzyme Tablet Analyzer STAT FAX 2100 (Awareness Technology, Palm City, FL, USA) at the Central Research Laboratory of the Pavlov Ryazan State Medical University.

The level of OS was determined by measuring the amount of carbonylated proteins in blood plasma using the Levine method, which involved the interaction of OMP with 2,4-dinitrophenylhydrazine. The resulting adducts were measured using a spectrophotometer (SF-2000; OKB Spectr, St. Petersburg, Russia). Then, the area under the curve of the absorption spectrum of spontaneous OMP was determined [15].

Statistical processing and graphing were performed using the Statistica 10 (StatSoft, Tulsa, OK, USA) and GraphPad Prism 9.0 (GraphPad Software, Boston, MA, USA) software. The conformity of the samples to normal distribution was checked using the Shapiro–Wilk criterion. Because the distribution did not meet normality assumptions, the Kruskal–Wallis and Mann–Whitney tests with Benjamini–Krieger–Yekutieli correction for multiple comparisons were used to identify differences

between independent groups. The Spearman rank correlation coefficient (r_s) was used to analyze the relationships between the indicators. Statistical significance was determined at a probability of the null hypothesis of no differences $p < 0.05$.

Results

No statistically significant correlations between the level of markers of systemic inflammation and OS in blood plasma ($p \geq 0.05$) were detected in the group of volunteers without respiratory diseases.

However, in the groups of patients with BA, COPD, and ACO, a statistically significant increase in the level of markers of systemic inflammation and OS in blood plasma was observed compared with the control group. Patients with COPD and ACO had the highest levels of proinflammatory cytokines. Furthermore, a higher level of protein carbonylation was detected in patients with COPD (Fig. 1).

The results of the correlation analysis of systemic inflammation and OS indices are shown in Table 2.

This study detected statistically significant correlations between the level of markers of systemic inflammation and the level of spontaneous protein oxidative modification (SPOM) in the ACO, BA, and COPD groups. Direct medium-strength correlations between IL-6 concentration and SPOM were detected in the ACO and BA groups, whereas a strong correlation was observed in the COPD group.

Direct medium-strength correlations between IL-8 concentration and SPOM were detected in the ACO and COPD groups, whereas a weak correlation was observed in the BA group.

Moreover, direct medium-strength correlations between TNF α concentrations and SPOM were detected in the ACO and BA groups.

To evaluate the impact of adipose tissue on systemic inflammation and protein oxidative damage, we investigated these parameters in subgroups categorized by BMI. Our findings indicate that excessive body weight in healthy volunteers is associated with increased levels of IL-6 (Table 3). The remaining parameters were similar across all subgroups. In patients with BA, a statistically significant association between excessive body weight and increased concentration of proinflammatory cytokines and level of SPOM in plasma was observed (refer to Table 3).

When comparing indicators in subgroups of COPD patients, patients with excessive body weight had statistically significant differences in the levels of IL-6, IL-8, and SPOM. However, the TNF α content was comparable in the study subgroups (Table 3).

The subgroups of patients with ACO, categorized by BMI, showed a statistically significant increase in the levels of IL-6 and TNF α (refer to Table 3).

When comparing the contribution of differences between the investigated parameters in ACO subgroups depending on smoking and excessive body weight, smoking was associated with a higher level of carbonylated proteins, whereas excessive body weight was associated with a 1.33-fold higher IL-6 index (Fig. 2).

Discussion

During the exacerbation period, patients with BA, COPD, and ACO had significantly higher levels of proinflammatory cytokines in their plasma than those in Group 4 (refer to Fig. 1). The levels of IL-6 in the blood plasma of the group of volunteers without respiratory diseases were 7.1-fold lower than those of the BA group, 9-fold lower than those of the COPD group, and 9.1-fold lower than those of the ACO group. Meanwhile, the levels of IL-8 in the blood plasma of the group of volunteers without respiratory diseases were 3.2-fold lower than those of the BA group, 3.3-fold lower than those of the COPD group, and 3.21-fold lower than those of the ACO group.

The levels of TNF α in the blood plasma of the group of volunteers without respiratory diseases were significantly lower than those of the BA group (1.8-fold), COPD group (2.54-fold), and ACO group (1.9-fold).

The evaluation of carbonylated proteins in blood plasma showed a significant increase in patients with BA (2.9-fold), COPD (5-fold), and ACO (2.72-fold) compared with the group of volunteers without respiratory diseases.

The results obtained do not contradict the data in similar studies [9, 16].

The level of carbonylated proteins increased, reflecting the intensity of oxidative damage to tissue proteins during disease exacerbation [11, 15]. Patients with COPD had the highest level of carbonylated proteins in blood plasma compared with the other groups (1.72-fold more than the BA group and 1.83-fold more than the ACO group), which can be attributed to several factors. Smoking is one of the most likely causes, as it can lead to local and systemic effects associated with inflammatory response and oxidative damage [17]. Furthermore, respiratory insufficiency, which causes hypoxemia and tissue hypoxia, is a significant factor that aggravates systemic OS [11].

In this study, the ACO and COPD groups were observed to have similar levels of systemic inflammatory response, as determined by the concentra-

Table 3. Levels of systemic inflammation and oxidative stress in subgroups categorized by body mass index (BMI)

Group	Index	BMI	n	Median	Q_1	Q_3	p
Volunteers without respiratory diseases	IL-6, pg/mL	<25	11	0,51	0,36	0,88	0,038
	IL-6, pg/mL	>25	30	0,80	0,61	1,43	
	IL-8, pg/mL	<25	11	21,10	8,32	30,18	0,803
	IL-8, pg/mL	>25	30	18,9	12,60	34,79	
	TNF α , pg/mL	<25	11	5,20	3,40	6,00	0,791
	TNF α , pg/mL	>25	30	4,60	3,65	5,55	
	SPOM, OD/mL	<25	11	77,94	56,77	145,29	0,918
	SPOM, OD/mL	>25	30	79,37	53,38	125,41	
Bronchial asthma	IL-6, pg/mL	<25	12	1,4	1,08	1,69	<0,001
	IL-6, pg/mL	>25	24	5,84	5,32	8,11	
	IL-8, pg/mL	<25	12	32,77	8,44	35,16	<0,001
	IL-8, pg/mL	>25	24	65,82	62,78	72,12	
	TNF α , pg/mL	<25	12	4,25	2,80	6,45	<0,001
	TNF α , pg/mL	>25	24	8,90	8,58	9,43	
	SPOM, OD/mL	<25	12	217,44	131,81	253,37	0,03
	SPOM, OD/mL	>25	24	236,78	217,41	287,96	
COPD	IL-6, pg/mL	<25	19	6,35	5,78	6,65	<0,001
	IL-6, pg/mL	>25	10	16,15	14,40	16,96	
	IL-8, pg/mL	<25	19	64,10	63,39	64,80	0,001
	IL-8, pg/mL	>25	10	82,03	72,45	85,81	
	TNF α , pg/mL	<25	19	12,20	9,40	13,00	0,69
	TNF α , pg/mL	>25	10	12,25	9,25	13,15	
	SPOM, OD/mL	<25	19	325,20	267,20	395,59	0,005
	SPOM, OD/mL	>25	10	548,42	439,10	602,48	
ACO	IL-6, pg/mL	<25	13	5,96	5,93	6,40	<0,001
	IL-6, pg/mL	>25	17	8,20	6,90	8,60	
	IL-8, pg/mL	<25	13	62,6	62,20	63,40	0,051
	IL-8, pg/mL	>25	17	63,5	63,08	64,04	
	TNF α , pg/mL	<25	13	8,40	8,20	8,60	0,002
	TNF α , pg/mL	>25	17	9,60	9,10	10,40	
	SPOM, OD/mL	<25	13	210,03	161,50	287,94	0,60
	SPOM, OD/mL	>25	17	229,37	188,38	250,61	

Note: The p value reflects the level of statistical significance of the differences in subgroups categorized by BMI. IL, interleukin; TNF α , tumor necrosis factor α ; SPOM, spontaneous protein oxidative modification; OD, optical density; COPD, chronic obstructive pulmonary disease; ACO, asthma–COPD overlap.

tion of IL-6 in blood plasma. However, the ACO group exhibited a lower level of SPOM (1.83-fold compared with that of the BA group) and a weaker correlation between the intensity of systemic inflammation and the severity of oxidative tissue damage compared with the COPD group (Fig. 1 and Table 2).

The level of IL-8 in the ACO group was similar to that in the BA group and lower than that in the COPD group (by 2.7%). Therefore, patients with ACO, unlike those with COPD, exhibited a lower intensity of OS, which is consistent with those reported in the literature [1]. Perhaps, this phenomenon is associated with the regular use of inhaled glucocorti-

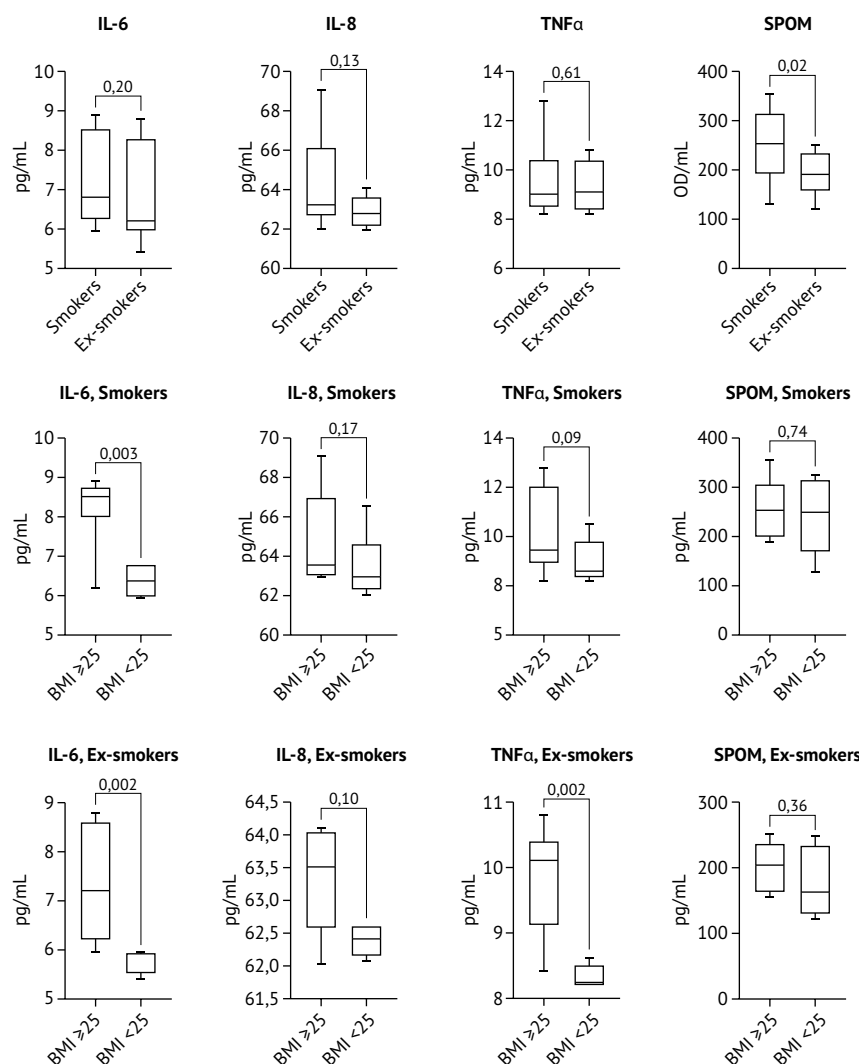


Fig. 2. Assessment of systemic inflammation and OS markers in the study subgroups of patients with combined BA and COPD based on the factors “smoking” and “excessive body weight.” The p values are presented as Me [Q_1 ; Q_3]. SPOM, spontaneous protein oxidative modification; IL, interleukin; TNFα, tumor necrosis factor α. Smokers ($n = 16$), a subgroup who were active smokers at the time of enrollment, of whom 8 had a BMI ≥ 25 kg/m² and 8 had a BMI < 25 kg/m². Ex-smokers ($n = 14$), a subgroup who quit smoking 5 years ago, with 9 having a BMI ≥ 25 kg/m² and 5 having a BMI < 25 kg/m².

coids at medium and high doses, which leads to a decrease in the level of proinflammatory cytokines and the expression of cell adhesion molecules that impede the migration of inflammatory cells into tissues.

Excessive body weight is currently receiving considerable attention as a factor that can modify the inflammatory response [18]. Therefore, we evaluated the indicators of systemic inflammation based on BMI.

Volunteers without respiratory diseases and with a BMI ≥ 25 kg/m² had 1.57-fold higher levels of IL-6 in blood plasma than those with a BMI < 25 kg/m². This difference could reflect the adaptive processes related to metabolism and the contribution of excess body weight to the development of low-intensity systemic inflammation [19].

Notably, in patients with BA and BMI ≥ 25 kg/m², the higher levels of IL-8 (twofold) and TNFα (twofold) likely reflect the neutrophilic inflammation characteristic of the obese BA phenotype [20].

Similarly, excessive body weight in patients with COPD was associated with higher levels of IL-8 (1.3-fold) and carbonylated proteins (1.7-fold), possibly indicating an increased neutrophilic inflammatory process [21, 22].

When cytokine concentrations were assessed in patients with BMI < 25 kg/m² and BMI ≥ 25 kg/m², the levels of IL-6 in blood plasma were determined to be higher in the ACO (1.38-fold), BA (4.17-fold), and COPD (2.54-fold) groups (refer to Table 3). The TNFα content was higher in patients with ACO

(1.14-fold) and BA (2.09-fold) with BMI > 25 kg/m² (refer to Table 3). These results support the idea that excessive body weight influences systemic inflammation parameters in patients with ACO [9].

Smoking is a well-investigated factor that can induce OS and subsequent inflammation [10, 13]. Therefore, the higher level of carbonylated proteins in blood plasma in the subgroup of smokers with ACO, as determined in this study, is consistent with those reported in the literature [10, 11, 13]. The similarity in the content of proinflammatory cytokines between the subgroups of smokers and ex-smokers indicates that smoking cessation alone may not be sufficient to reduce the inflammatory process. This finding requires further confirmation.

The 1.33-fold higher level of IL-6 in the subgroup of smokers with BMI ≥ 25 kg/m² (8.5 [7.98; 8.75] pg/mL) than that in the subgroup of smokers with BMI < 25 kg/m² (6.38 [5.96; 6.80] pg/mL) indicates that excess adipose tissue may contribute to the modification of the pattern of inflammation. This finding is consistent with those reported in the literature [21, 22].

The limitations of this study should be acknowledged, particularly the small sample size because of its pilot nature. This limitation complicates the detailed assessment of the relationship between excess body weight and its contribution to the potentiation of systemic inflammation. However, the data obtained in this study complement previously identified patterns and highlight the importance of further research into the influence of adipose tissue on the course of chronic inflammatory respiratory diseases.

Conclusions

1. The correlation between the intensity of systemic inflammation during an exacerbation in patients with ACO and the intensity of oxidative damage was confirmed by a direct medium-strength correlation strength between the concentration of proinflammatory cytokines and the level of carbonylated proteins in blood plasma. The most pronounced correlation was observed between the concentration of IL-6 and the level of SPOM.

2. Excess body weight in patients with ACO, BA, and COPD is associated with enhanced inflammatory response and OS, as manifested by increased concentrations of proinflammatory cytokines and levels of carbonylated proteins in blood plasma.

3. Smoking cessation in patients with ACO and BMI ≥ 25 kg/m² should be combined with measures to correct excessive body weight to reduce the intensity of systemic inflammation.

Authors' contribution. S.V.F., conceptualization, collection of materials for the study, laboratory research, statistical analysis, search for publications on the topic of the article, and writing the text of the article; O.M.U., conceptualization, peer review of information, editing of the text of the article, and supervising the study; E.S.B., laboratory research, statistical analysis, search for publications on the topic of the article, and editing of the text of the article; S.V.B., collection of materials for the study, editing of the text of the article, and peer review of information; L.V.K., collection of materials for the study, editing of the text of the article, and peer review of information.

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REFERENCES

1. Mekov E, Nuñez A, Sin DD, Ichinose M, Rhee CK, Maselli DJ, Coté A, Suppli Ulrik C, Maltais F, Anzueto A, Miravittles M. Update on asthma-COPD overlap (ACO): A narrative review. *Int J COPD*. 2021;16:1783–1799. DOI: 10.2147/COPD.S312560.
2. Hosseini M, Almasi-Hashiani A, Sepidarkish M. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respir Res*. 2019;20(1):229. DOI: 10.1186/s12931-019-1198-4.
3. Miethe S, Karsonova A, Karaulov A, Renz H. Obesity and asthma. *J Allergy Clin Immunol*. 2020;146(4):685–693. DOI: 10.1016/j.jaci.2020.08.011.
4. Faletrova SV, Korshunova LV, Belskikh ES. Clinical and functional features of chronic obstructive lung disease in patients with obesity. *Eruditio Juvenium*. 2018;6(3):439–447. (In Russ.) DOI: 10.23888/HMJ201863439-447.
5. Drapkina OM, Avdeev SN, Budnevsky AV, Ovsyannikov ES, Kontsevaya AV, Drobysheva ES. Nutrition status and obesity paradox in chronic obstructive pulmonary disease. *Voprosy pitaniya*. 2021;90(6):42–49. (In Russ.) DOI: 10.33029/0042-8833-2021-90-6-42-49.
6. Ovsyannikov ES, Budnevsky AV, Shkatova YS. Assessment of effectiveness of training of respiratory musculature in patients with chronic obstructive pulmonary disease and obesity. *IP Pavlov Russian Medical Biological Herald*. 2019;27(3):367–374. (In Russ.) DOI: 10.23888/PAV-LOVJ2019273367-374.
7. Peltola L, Päätsi H, Harju T. COPD Comorbidities Predict High Mortality — Asthma-COPD-Overlap Has Better Prognosis. *COPD: Journal of Chronic Ob-*

structive Pulmonary Disease. 2020;17(4):366–372. DOI: 10.1080/15412555.2020.1783647.

8. Gava G, Núñez A, Esquinas C, Sarasate M, Loeb E, Pirina P, Miravittles M, Barrecheguren M. Analysis of blood biomarkers in patients with Chronic Obstructive Pulmonary Disease (COPD) and with Asthma-COPD Overlap (ACO). *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2020;17(3):306–310. DOI: 10.1080/15412555.2020.1761314.

9. Ghosh N, Choudhury P, Kaushik SR, Arya R, Nanda R, Bhattacharyya P, Roychowdhury S, Banerjee R, Chaudhury K. Metabolomic fingerprinting and systemic inflammatory profiling of asthma COPD overlap (ACO). *Respir Res*. 2020;21(1):126. DOI: 10.1186/s12931-020-01390-4.

10. Marwick JA, Ito K, Adcock IM, Kirkham PA. Oxidative stress and steroid resistance in asthma and COPD: Pharmacological manipulation of HDAC-2 as a therapeutic strategy. *Expert Opin Ther Targets*. 2007;11(6):745–755. DOI: 10.1517/14728222.11.6.745.

11. Sies H, Berndt C, Jones DP. Oxidative stress. *Annu Rev Biochem*. 2017;86:715–748. DOI: 10.1146/annurev-biochem-061516-045037.

12. Nikolova G, Ilieva V, Karamalakova Y, Zheleva A, Gadjeva V. Comparative study of oxidative status in blood of asthmatic patients. *Comp Clin Pathol*. 2018;27:1057–1063. DOI: 10.1007/s00580-018-2701-x.

13. Belskikh ES, Uryasev OM, Zvyagina VI, Faletrova SV. Development of secondary mitochondrial dysfunction of blood mononuclear leukocytes in patients with chronic obstructive pulmonary disease and chronic bronchitis. *Kazan Medical Journal*. 2018;99(5):741–747. (In Russ.) DOI: 10.17816/KMJ2018-741.

14. Tikhova GP. Planning clinical research. question #1: how to calculate enough sample volume? *Regional Anesthesia and Acute Pain Management*. 2014;(3):57–63. (In Russ.) EDN: SXYCWF.

15. Fomina MA, Abalenikhina YuV. *Okislitel'naya modifikatsiya belkov tkaney pri izmenenii sinteza oksida*.

azota. (Oxidative modification of tissue proteins by changing the synthesis of nitric oxide.) Moscow: GEOTAR-Media; 2018. 192 p. (In Russ.)

16. Kubysheva N, Boldina M, Eliseeva T, Soodaeva S, Klimanov I, Khaletskaya A, Bayrasheva V, Solov'yev V, Villa-Vargas LA, Ramírez-Salinas MA, Salinas-Rosales M, Ovsyannikov DY, Batyrshin I. Relationship of serum levels of IL-17, IL-18, TNF- α , and lung function parameters in patients with COPD, asthma-COPD overlap, and bronchial asthma. *Mediators Inflamm*. 2020;12:4652898. DOI: 10.1155/2020/4652898.

17. Colombo G, Aldini G, Orioli M, Giustarini D, Gornati R, Rossi R, Colombo R, Carini M, Milzani A, Dalle-Donne I. Water-Soluble α , β -unsaturated aldehydes of cigarette smoke induce carbonylation of human serum albumin. *Antioxid Redox Signal*. 2010;12(3):349–364. DOI: 10.1089/ars.2009.2806.

18. Scott HA, Wood LG, Gibson PG. Role of obesity in asthma: mechanisms and management strategies. *Curr Allergy Asthma Rep* 2017;17(8):53. DOI: 10.1007/s11882-017-0719-9.

19. Sindhu S, Thomas R, Shihab P, Sriraman D, Behbehani K, Ahmad R. Obesity is a positive modulator of IL-6R and IL-6 expression in the subcutaneous adipose tissue: Significance for metabolic inflammation. *PLoS One*. 2015;10(7):e0133494. DOI: 10.1371/journal.pone.0133494.

20. Budnevsky AV, Malyshev EY, Ovsyannikov ES, Drobysheva ES. Asthma and metabolic syndrome: Clinical and pathogenetic relationships. *Therapeutic archive*. 2015;87(10):110–114. (In Russ.) DOI: 10.17116/TER-ARKH20158710110-114.

21. Karczewski J, Śledzińska E, Batur A, Jończyk I, Maleszko A, Samborski P, Begier-Krasińska B, Dobrowolska A. Obesity and inflammation. *Eur Cytokine Netw*. 2018;29(3):83–94. DOI: 10.1684/ecr.2018.0415.

22. Herrero-Cervera A, Soehnlein O, Kenne E. Neutrophils in chronic inflammatory diseases. *Cell Mol Immunol*. 2022;19(2):177–191. DOI: 10.1038/s41423-021-00832-3.

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