

Excess Body Weight and Markers of Systemic Inflammation in Exacerbation of Asthma-COPD overlap

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ABSTRACT

Aim: To compare the level of markers of systemic inflammation (IL6, IL8, TNF α) in patients with bronchial asthma-COPD overlap (ACO) with normal and excess body weight during exacerbation.

Methods: The study included 71 people, of whom 30 were patients with a combination of bronchial asthma and COPD (Asthma-COPD Overlap) in the exacerbation phase and 41 conditionally healthy volunteers. All the subjects were divided into subgroups depending on the body weight index (BMI) and the presence of abdominal obesity (AO). Blood sampling was carried out on the second day, prior to the beginning of treatment with systemic glucocorticosteroids. The plasma concentration of IL6, IL8, TNF α was determined by enzyme immunoassay.

Results: In group of patients with exacerbation of the ACO (n=30) the level of plasma markers of system inflammation was higher in comparison with indicators of control group (n=41) (IL-6 by 9.1 times, p<0.05; IL-8 by 3.2 times, p<0.05; TNF- α by 1.9 times, p<0.05). Patients with ACO and AO (n=17) showed an increase in IL6 concentration and TNF α in comparison with ACO group without AO (n=13) on 37.6% (p<0.05) and 15.9% (p<0.05) respectively. Both excess body weight and AO was associated with an increase in plasma concentration of IL-6 and TNF- α in patients with ACO compared to the group of ACO with normal body weight per 37.6% and 14.3%, respectively (p<0.05).

Conclusion: Overweight in patients with exacerbation of ACO is associated with an increase in the level of IL-6 and TNF- α .

Keywords: Asthma-COPD overlap, IL-6, TNF- α , overweight.

INTRODUCTION

Over the past decade, many studies have been devoted to the problem of combined pathology and comorbidity. It was found that already at the young age group (25-44 years according to the WHO classification) it is difficult to find patients with one disease, while in the older age group, patients usually have two or more diseases¹. Therefore, the search for new diagnostic methods, innovative therapeutic approaches and preventive measures when working with a comorbid patient is becoming increasingly relevant^{1,2,3}.

Chronic diseases of the respiratory system are widespread in the world and are one of the main causes of premature death of the adult population^{4,5}. According to epidemiological studies in the world 235 million people suffer from bronchial asthma (BA), while about 400 thousand patients die from asthma annually in the world^{6,7}. In 2006, GINA materials emphasized that not only obesity, but also overweight is an independent risk factor in BA. In 2018, five BA phenotypes were distinguished in GINA, among which bronchial asthma with obesity was identified, which is more difficult to control and has a worse prognosis^{8,9}. For BA, in an uncontrolled course, an incompletely reversible bronchial obstruction is characteristic, which determines the importance of achieving control of the disease. An important feature of BA in obese patients is the predominance of neutrophilic inflammation, which reduces the effectiveness of standard anti-inflammatory therapy¹⁰.

Another socially significant common chronic respiratory disease is chronic obstructive pulmonary disease (COPD). According to WHO data, 251 million cases of COPD were reported worldwide in 2016. In 2015,

more than 3 million people died of the disease in the world¹¹. It has been proved that patients with COPD with excess body weight have a greater reduction in restriction and obstructive indicators of respiratory function, lower quality of life than patients with normal body weight¹².

A separate problem of diagnosis and therapy of chronic respiratory diseases is the combination of BA and COPD, in connection with which the last 10 years the prevalence of asthma-COPD overlap has been actively assessed, which is reflected in the national recommendations on COPD in the Spain and Russia¹³⁻¹⁵. In 2015, a multi-center study the SUPPORT was carried out in Russia, one of the goals of which was to analyze the distribution of COPD patients by phenotypes. As a result, the epidemiology of the combination of BA and COPD was found to be 13% in the population, which corresponds to the results of epidemiological studies in the USA and Spain¹³⁻¹⁸. In this category of patients, uncontrolled course of obstructive diseases occurs more often. In this regard, the combination of BA and COPD in one patient imposes special requirements for diagnosis, maintenance tactics, due to mutual burden.

Along with respiratory diseases, a significant challenge for health systems is the significant incidence of obesity. According to WHO in 2016, more than 1.9 billion adults (almost 13%) were overweight worldwide. Of these, more than 650 million were obese. At the same time, the number of overweight people continues to grow steadily every year¹⁹. Thus, the widespread worldwide prevalence of BA, COPD and obesity results in a high probability of combining three nosologies in one patient.

Currently, a number of studies have obtained data that such diseases as BA, COPD, obesity are associated with an increased level of circulating pro-inflammatory cytokines in the blood plasma, among which IL-6, IL-8, TNF- α are of the greatest importance²⁰⁻²⁵. However, there are practically no studies on the effect of excess body weight, as a potential source of pro-inflammatory cytokines, on concomitant chronic obstructive diseases.

In this regard, the purpose of the study was to compare biomarkers systemic inflammation in patients with a combination of BA and COPD with normal and excess body weight during exacerbation.

METHODS

The pilot study was performed in the period from 2017 to 2018 at the Department of Faculty Therapy with course of Therapy FDPO of the Ryazan State Medical University. The study was approved by Local Ethics Committee of Ryazan State Medical University and complies with the requirements of Good Clinical Practice (GCP) and the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

The basis for inclusion in the study was signed informed consent. The inclusion criteria for control group were age from 50 to 70 years, the absence of chronic respiratory diseases. The inclusion criteria for patients with asthma-COPD overlap (ACO) were age from 50 to 70 years, existence in the anamnesis of the established diagnosis of ACO, a disease during aggravation. ACO is diagnosed with 3 signs characteristic of BA and three signs characteristic of COPD [9]. Exclusion criteria for all groups were persons are younger 50 and 70 years, pharmacotherapy system glucocorticosteroids prior to the research, secondary obesity, the alimentary and constitutional obesity 4 degrees, other pathology of respiratory organs, cardiovascular pathology with chronic heart failure \geq are more senior than II And stages, diabetes, other serious associated diseases and their complications, alcoholism, drug addiction.

The minimal sample size was calculated with the statistical assumptions of 5% alpha error and 95 % confidence interval taking frequency of decreased IL-6 least on 20% to be 90% amongst patients with ACO.

All patients and healthy respondents were given a clinical examination (collection of anamneses, examination, evaluation of external breathing function with the help of a MicroLab spirometer), anthropometry. BMI was calculated by formula: BMI = body weight, kg/growth, m². Evaluation of fat tissue distribution - waist volume (OT) was carried out according to the criteria of the International Diabetes Federation (IDF) according to the consensus on metabolic syndrome.

Laboratory tests were performed before treatment began. The determination of the concentration of IL-6, IL-8, TNF- α was carried out at the Central Research Laboratory of Ryazan State Medical University on the STAT FAX 2100 Immunoenzyme Plate Analyzer by immunoassay using HUMAN IL-8/NAP-1, HUMAN IL-6, HUMAN TNF- α ELISA kits.

The study involved 71 people divided into two groups. The ACO group included 30 of patients with ages 57 to 65 years (average age 60,5 \pm 4.7). Among them 13.3% (n = 4), women, 86.7% (n = 26) men. Depending on the size of the waist circle (WC) characterizing existence or absence the abdominal obesity (AO), patients with ACO were divided into subgroups 1A (n=17, WC \geq 94 by cm for men and \geq 80 cm for women) and 1B (n=13, WC <94 cm for men and <80 cm for women). Depending on indicators of body mass index (BMI) patients were divided into subgroups 1C (n = 17, BMI \geq 25kg/m²) and 1D (n=13, BMI <25kg/m²). Patients with AO had a BMI \geq 25 kg/m², and individuals without AO had a BMI<25 kg/m², respectively.

The control group consisted of 41 respondents between the ages of 50 and 70 (average age 60.5 \pm 4.1). Of these, 78% (n=32) are female, 22% (n=9) are male. The control group is divided into 4 subgroups taking into account BMI and WC: 2A (n=31, WC \geq 94 cm for men and \geq 80 cm for women) and 2B (n=10, WC<94 cm for men and <80 cm for women), C (n = 30, IMT \geq 25 25kg/m²) and 2D (n=11, BMI <25kg/m²). Groups were comparable in age. The ACO group was dominated by men (86.7%). Women (78%) were more likely to meet among healthy respondents.

Statistical processing was carried out using parametric and non-parametric methods using the standard "Statistica 10" software package. Quantitative values are presented in the form of median (Me) and apartment scales (first and third quartiles). Qualitative variables are described by absolute and relative frequencies (percentages). A quantitative comparison of the groups was performed using the non-parametric Mann-Whitney (U) criterion. The normal distribution of samples, determined by the Shapiro-Wilk and Kolmogorov-Smirnov method, is not recorded. Analysis of statistical (correlation) relationships between anthropometric data and concentration levels of biochemical indices under study is carried out by calculation of Spirman 's rank correlation coefficient. The differences at p < 0.05 were considered statistically significant.

RESULTS

From the results it follows that in the group of patients with OA, the level of markers of systemic inflammation in the blood was significantly higher compared with the control group (IL-6 9.1 times, IL-8 3.2 times, TNF- α 1.9 times) (Tab. 1).

In subgroups of the healthy volunteers divided depending on BMI or WC, the studied levels of cytokines statistically significantly did not differ (p \geq 0.05).

The presence of AO in patients with ACO was found to be associated with a statistically significant increase in plasma IL-6 and TNF- α concentrations relative to those in the ACO group without abdominal obesity on 37.6% and 15.9%, respectively (p < 0.05). At the same time, the presence of AO did not statistically significantly affect the level of IL-8 (p \geq 0.05) (tab. 2).

When assessing the effect of overweight on the level of pro-inflammatory cytokines, it was found that in the overweight group, a statistically significant increase in plasma concentrations of IL-6 and TNF- α was observed in patients with ACO compared to the ACO group with normal

body weight by 37.6 % and 14.3%, respectively. The level of IL-8 in groups divided by BMI did not statistically significantly differ.

Correlation analysis revealed a relationship between moderate strength between the concentration of IL-6 and TNO- α in blood plasma with the presence of excess body

weight ($p < 0.05$), as well as moderate strength, the relationship between RT and the level of pro-inflammatory cytokines ($p < 0.05$). The relationship between the level of IL-8 and the studied anthropometric indicators was insignificant ($p \geq 0.05$) (Table 3).

Table 1: Serum Cytokine Levels of Examined Persons

Biomarkers	ACO(group 1), n=30	Control (rpyinna 2), n=30	P value
	Me[Q1;Q3]		
IL-6, pg/ml	6.8[5.96;8.4]	0.75[0.51;1.08]	0.00001
IL-8,pg/ml	63.1[62.6;64.04]	19.66[12.1;32.64]	0.00001
TNF- α ,pg/ml	9.1[8.4;10.4]	4.8[3.6;5.6]	0.000001

Table 2: Serum cytokine levels in patients with ACO depending on anthropometric parameters (n=30)

Biomarkers	Subgroup A n=17	Subgroup B n=13	P value	Subgroup C n=17	Subgroup D n=13	P value
	Me[Q1;Q3]			Me[Q1;Q3]		
IL-6, pg/ml	8.2[6.63;8.6]	5.96[5.93;6.8]	0.0016	8/2[6.9;8.6]	5.96 [5.93;6.4]	0.0003
IL-8,pg/ml	63.53[63.09;64.04]	62.6[62.2;63.4]	0.0614	63.5[63.08;64.04]	62.6[62.2;63.4]	0.051
TNF- α ,pg/ml	9.85[9.1;10.6]	8.5[8.2;8.7]	0.0032	9.6[9.1;10/4]	8.4[8.2;8.6]	0.0022

Table3.: Correlation of anthropometric parameters and cytokines in patients with ACO

Spearman's rank correlations, r_s ; n=30	IL-6, pg/ml	TNF- α pg/ml	IL-8 pg/ml
BMI, kg/m ²	$r_s=0.57$; $p=0.00106$	$r_s=0.44$; $p=0.01635$	$r_s=0.23$; $p=0.22925$
WC, cm	$r_s=0.47$; $p=0.00895$	$r_s=0.43$; $p=0.01721$	$r_s=0.18$; $p=0.34218$

DISCUSSION

When studying indicators of the level of systemic blood inflammation, patients with ASO showed a significant increase in the level of IL-6, IL-8, TNF- α compared with the control group, which, most likely, reflected the development of a systemic inflammatory process during exacerbation of the disease.

A comparison of the level of pro-inflammatory cytokines among ASO patients with normal and overweight allowed us to establish that overweight is accompanied by an increase in the levels of IL-6 and TNF- α . These changes probably reflected the modifying effect of adipose tissue on the nature of systemic inflammation with a combination of bronchial asthma and COPD, which does not contradict the results of previous studies on the effect of excess body weight on both AD and COPD^{3,20-25}. This is confirmed by positive correlations of moderate strength between the studied anthropometric indicators of overweight and the levels of the studied pro-inflammatory cytokines.

The absence of differences in the level of IL-8 in the blood in patients in groups divided depending on the presence of excess body weight and abdominal obesity probably reflects the absence of a significant contribution of adipose tissue to the production of a factor that plays an important role in neutrophil chemotaxis under conditions of exacerbation of ASO, which is confirmed by the absence reliable correlation between the studied indicators.

Thus, overweight in patients with exacerbation of ACO can be considered as a factor that can aggravate the course of the underlying disease. In this regard, the use of a therapeutic strategy aimed at reducing and controlling body weight can probably bring a positive effect associated with a decrease in the severity of systemic inflammation, which requires additional study in patients with combined bronchial obstructive pathology.

CONCLUSION

Exacerbation of the of asthma-chronic obstructive pulmonary disease overlap is associated with an increased the level of IL-6, IL-8, TNF- α in the blood. Overweight in patients with exacerbation of ACO is associated with an increase in the level of IL-6 and TNF- α . Blood IL-8 level does not depend on body weight in patients with exacerbation of ACO.

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