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# INFLUENCE OF INTESTINAL PERMEABILITY AND ENDOTOXINEMIA ON THE COURSE OF ASTHMA IN OBESE PATIENTS

***M.A. Grakhova[1,2]*, I.A. Troshina[1], T.I. Golubeva[1], A.M. Pavlova[1], A.P. Pluzhnikova***
*Tyumen State Medical University,*
*Regional Clinical Hospital No. 1, Tyumen, Russian Federation*

# ВЛИЯНИЕ КИШЕЧНОЙ ПРОНИЦАЕМОСТИ И ЭНДОТОКСИНЕМИИ НА ТЕЧЕНИЕ БРОНХИАЛЬНОЙ АСТМЫ У ПАЦИЕНТОВ С ОЖИРЕНИЕМ

***М.А. Грахова[1,2]*, И.А. Трошина[1], Т.И. Голубева[1], А.М. Павлова[1], А.П. Плужникова[2]***
*[1]Тюменский государственный медицинский университет,*
*[2]Областная клиническая больница № 1, г. Тюмень, Российская Федерация*

**Objective.** To study the characteristics of asthma with a severe course in obese patients and to evaluate the relationship of the level of intestinal endotoxin (ET) and fecal zonulin with clinical, laboratory and instrumental indicators in such patients.
**Materials and methods.** The study included 98 patients with asthma combined with obesity (group 1 – mild asthma ($n = 47$), group 2 – severe asthma ($n = 51$)) and 45 obese patients without asthma composed the comparison group. A complete standard examination and tests were conducted in all the patients. Intestinal ET, fecal zonulin, TNF-α, IFN-γ, IL-4, 6, 10, 17, total IgE levels were assessed as well. The IBM SPSS Statistics 26.0 applica-


tel. +7 919 959 10 79
e-mail: mari.grahova@yandex.ru
[Grakhova M.A. (*contact person) – Allergist-Immunologist, Assistant of the Department of Hospital Therapy with the Course of Endocrinology, ORCID: 0000-0002-1657-0695; Troshina I.A. – DSc (Medicine), Associate Professor, Head of the Department of Hospital Therapy with the Course of Endocrinology, ORCID: 0000-0002-7772-8302; Golubeva T.I. – PhD (Medicine), Associate Professor of the Department of Hospital Therapy with the Course of Endocrinology, Gastroenterologist, ORCID: 0000-0002-3909-5364; Pavlova A.M. – Assistant of the Department of Hospital Therapy with the Course of Endocrinology, Endocrinologist, ORCID: 0000-0002-2172-111X; Pluzhnikova A.P. – Pulmonologist, ORCID: 0009-0000-3450-2816].


тел. +7 919 959 10 79
e-mail: mari.grahova@yandex.ru
[Грахова М.А. (*контактное лицо) – врач аллерголог-иммунолог, ассистент кафедры госпитальной терапии с курсом эндокринологии, ORCID: 0000-0002-1657-0695; Трошина И.А. – доктор медицинских наук, доцент, заведующая кафедрой госпитальной терапии с курсом эндокринологии, ORCID: 0000-0002-7772-8302; Голубева Т.И. – кандидат медицинских наук, врач-гастроэнтеролог, доцент кафедры госпитальной терапии с курсом эндокринологии, ORCID: 0000-0002-3909-5364; Павлова А.М. – врач-эндокринолог, ассистент кафедры госпитальной терапии с курсом эндокринологии, ORCID: 0000-0002-2172-111X; Плужникова А.П. – врач-пульмонолог, ORCID: 0009-0000-3450-2816].

tion software package was used for statistical calculations. The results were considered as statistically significant at the level of $p$ <0,05.

**Results.** In patients of both groups, the average age of onset was 43 years. The median duration of BA characteristics was higher in patients of group 2: 14 [10; 19] years ($p$ = 0.013). In all groups, CRPhs values increased significantly and the highest ones were in patients with severe asthma ($p$ < 0.001). Significantly lower levels of FVC, FEV1, FEV1/FVC, IL-10 ($p$<0.001) with uncontrolled course of asthma ($p$ = 0.008) and rare control ($p$ = 0.009) occurred in patients of group 2. Higher levels of TNF-α, IFN-γ, IL-6,17, intestinal ET, fecal zonulin were revealed in patients of group 2 ($p$≤0.001). The level of fecal zonulin positively correlated with the level of intestinal ET in patients of group 2 ($p$<0.001, $rs$=0.813). In patients of group 2 direct correlations of the fecal zonulin and intestinal ET with BMI, WC, HC, WC/HC, lack of BA control, CRPhs, TNF-α, IL-6,17, IFN-γ, LDL were established and inverse correlations were with IL-10, HDL, FEV1, AST; a negative correlation of fecal zonulin levels with FVC was also revealed.

**Conclusions.** The obtained results allow us to speak about the existence of a clinical complex "severe asthma – obesity – intestinal endotoxemia and increased intestinal permeability" which is characterized by the predominance of pro-inflammatory markers, increased levels of intestinal ET and fecal zonulin, reduced function of external breathing.

**Keywords.** Severe bronchial asthma, obesity, intestinal endotoxin, zonulin.

**Цель.** Изучить особенности течения тяжелой бронхиальной астмы (БА) в сочетании с ожирением, а также оценить взаимосвязь уровня кишечного эндотоксина (ЭТ) и фекального зонулина с клинико-лабораторными и инструментальными показателями у данной когорты пациентов.

**Материалы и методы.** В исследование было включено 98 пациентов с БА в сочетании с ожирением (1-я группа – легкая БА ($n$ = 47), 2-я группа – тяжелая БА ($n$ = 51)) и 45 человек с ожирением без БА (группа сравнения). Всем пациентам выполнено комплексное стандартное обследование, а также определение уровня кишечного ЭТ, фекального зонулина, TNF-α, IFN-γ, IL-4, IL-6, IL-10, IL-17, IgE общего, аллергопробы по показаниям. Для статистической обработки данных использовался пакет программы IBM SPSS Statistics 26.0. Результаты оценивались как статистически значимые при уровне $p$ < 0,05.

**Результаты.** У пациентов 1-й и 2-й групп медиана возраста дебюта составила 43 года. Медиана продолжительности БА статистически значимо была выше у пациентов 2-й группы и составила 14 [10; 19] лет ($p$ = 0,013). В трех группах значения СРБhs существенно возрастали и были максимальными у пациентов с тяжелой БА ($p$ < 0,001). Значимо более низкие показатели ФЖЕЛ, $ОФВ_1$, $ОФВ_1$/ФЖЕЛ, IL-10 ($p$ < 0,001) с более частым неконтролируемым течением БА ($p$ = 0,008) и редким контролем ($p$ = 0,009) встречались у пациентов 2-й группы. Статистически значимо более высокие показатели TNF-α, IFN-γ, IL-6, IL-17, кишечного ЭТ, фекального зонулина были выявлены у пациентов 2-й группы ($p$ ≤ 0,001). Уровень фекального зонулина положительно коррелировал с уровнем кишечного ЭТ у пациентов 2-й группы ($p$ < 0,001; $rs$ = 0,813). Были установлены статистически значимые прямые корреляционные связи показателя фекального зонулина и кишечного ЭТ у пациентов 2-й группы с ИМТ, ОТ, ОБ, ОТ/ОБ, отсутствием контроля БА, СРБhs, TNF-α, IL-6, IL-17, IFN-γ, ЛПНП и обратные корреляционные связи с IL-10, ЛПВП, $ОФВ_1$, АСТ-тестом; также выявлена отрицательная корреляция уровня фекального зонулина с ФЖЕЛ.

**Выводы.** Полученные результаты позволяют говорить о существовании клинического комплекса «тяжелая БА – ожирение – кишечная эндотоксемия и повышенная проницаемость кишечника», который характеризуется преобладанием провоспалительных маркеров, повышением кишечного ЭТ и фекального зонулина, сниженной функцией внешнего дыхания.

**Ключевые слова.** Тяжелая бронхиальная астма, ожирение, кишечный эндотоксин, зонулин.

## INTRODUCTION

Bronchial asthma (BA) and obesity are widespread diseases, and in recent years there has been a significant increase in the syntropy of these two conditions. The identification of a separate phenotype of asthma with obesity indicates a significant contribu-

tion of obesity in the course of asthma1. According to research data, the "obese asthma" phenotype is characterized by a more severe course, low level of disease control, resistance to basic therapy, and frequent hospitalizations during exacerbations [1].

Severe asthma in combination with obesity is characterized by specific pathophysiological features of the inflammatory response, where the role of intestinal endotoxin, along with increased intestinal permeability, is insufficiently studied. Intestinal endotoxin is known to be associated with both neutrophilic and eosinophilic airway inflammation, airway hyperreactivity, and glucocorticosteroid resistance in asthma [2]. One of the modern directions considers the role of the intestinal microbiome and endotoxinemia in the formation of a more severe course of bronchial asthma in this group of patients. Zonulin is a protein that controls the permeability of the intestinal epithelial barrier [3]. Activation of the zonulin pathway provokes the development of leaky gut syndrome [4], and in combination with endotoxinemia, through the intestine-lung axis [5], it aggravates the course of bronchial asthma in obese patients.

The clinical complex "severe bronchial asthma – obesity – intestinal endotoxemia and increased intestinal permeability (increased zonulin levels)" is currently an object of active study in terms of revealing its pathogenetic comorbidity, prognostic risks of the course of diseases and determining patient management tactics.

## MATERIALS AND METHODS

A study was conducted at the State Budgetary Healthcare Institution of the Tyumen Region "OKB No. 1" and the Federal State Budgetary Educational Institution of Higher Education "Tyumen State Medical University" of the Ministry of Health of the Russian Federation involving 143 people (98 patients were diagnosed with bronchial asthma combined with obesity, 42 patients in the comparison group were diagnosed with obesity without bronchial asthma). Inclusion criteria for the study: age 18 years and older; duration of asthma for at least one year prior to inclusion in the study; verified diagnosis of mild and severe asthma; obesity of grades I and II (BMI from 30 to 39.9 kg/m$^2$); signed voluntary informed consents. Exclusion criteria for the study: bronchial asthma complicated by severe somatic diseases in the decompensation stage; BMI less than 30 kg / m$^2$ and more than 40 kg / m$^2$; other respiratory diseases; pregnancy and / or lactation; use of genetically engineered biological drugs; smoking of the patient at the time of inclusion in the study. According to the developed criteria, two main study groups were formed: Group 1 – mild asthma with obesity ($n$ = 47), Group 2 – severe asthma with obesity ($n$ = 51). The diagnosis, severity and level of asthma control were established in accordance with GINA 2023 and Russian clinical guidelines "Bronchial Asthma" (2021). The ACT (Asthma Control Test) questionnaire was used to assess the level of asthma control. The comparison group consisted of 45 patients with obesity of grades I and II (BMI from 30 to 39.9 kg / m$^2$) without bronchial asthma. The clinical and instrumental examination included: anthropometric examination, spirography with a bronchodilator (Spirolan device, Laname-

dica LLC, Russia); general clinical laboratory examinations, lipid spectrum (total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL)), and C-reactive protein (high-sensitivity method – hs) in blood serum were performed using a Beckman Coulter reagent kit (USA). The level of total IgE in blood plasma was measured using a set of test systems from the company NPO Diagnostic Systems (Russia). The study of TNF-α, IFN-α, IL-4, 6, 10 was carried out using a set of reagents from JSC Vector-Best JSC (Russia), the determination of the cytokine IL-17 was carried out using reagents from eBioscience (USA). The level of intestinal endotoxin in the systemic circulation was studied using the micro-LAL test (Hycult Biotech, Netherlands), the concentration of zonulin in feces was determined using the Immundiagnostik AG reagent kit (Germany). Skin allergy tests were performed using the scarification method (allergen extracts from NPO Mikrogen JSC, Russia). This study was conducted in accordance with the protocol approved by the local ethics committee at the Federal State Budgetary Educational Institution of Higher Education "Tyumen State Medical University" of the Ministry of Health of the Russian Federation on 09.09.2022. The IBM SPSS Statistics 26.0 software package was used for data processing. For descriptive statistics, the median (Me) and interquartile range [Q1; Q3] were used, where Q1 is the lower quartile (25 %) and Q3 is the upper quartile (75 %). When comparing quantitative indicators in the three study groups, the Kruskal-Wallis test with Bonferroni correction for multiple comparisons was used; in two groups, the Mann – Whitney U test was used. Categorical indicators in groups were compared using the $\chi^2$ Pearson criterion and Fisher's exact criterion. Analysis of correlation relationships was performed with the determination of the Spearman rank correlation coefficient (rs). The strength of correlations was assessed using the Chaddock scale. Differences were considered statistically significant at $p < 0.05$.

## RESULTS AND DISCUSSION

The study groups were comparable in terms of gender ($p = 0.628$), age ($p = 0.337$), anthropometric parameters (height ($p = 0.854$), weight ($p = 0.952$), BMI ($p = 0.727$), waist volume (WC) ($p = 0.275$), hip volume (HV) ($p = 0.367$), WC / HV index ($p = 0.171$)). The patients were predominantly female (more than 90 %). The median age of patients in the first group was 55 [50.5; 57.5] years, in the second – 63 [54; 67] years, in the comparison group – 61 [48; 66] years. When distributing patients by the degree of obesity and the type of fat deposition, patients with grade I obesity (51 % and more) and with the android type (WC / OB more than 0.85) of fat deposition (88 % of cases and more) predominated. In patients of groups 1 and 2, the median age of asthma onset was 43 years, which indicates a late onset of the underlying disease in combination with obesity and is consistent with data from other studies [6]. The median duration of asthma was statistically significantly ($p = 0.013$) higher in patients with severe asthma in combination with obesity and was 14 [10; 19] years, while in patients of group 1 it was 10 [7; 16] years,

which may indicate the effect of the duration of asthma on the severity of the disease [7].

An analysis of the incidence of concomitant diseases in three groups was conducted (Fig. 1). No statistically significant differences were found in the spectrum of concomitant pathology in patients in all three groups ($p > 0.05$). The most common concomitant pathology in patients with severe bronchial asthma combined with obesity was cardiovascular pathology (56.86 %), arterial hypertension (89.66 %); ENT diseases were less common – 41.18 % (AR – 80.96 %, CPRS The most common concomitant pathology in patients with severe bronchial asthma combined with obesity was cardiovascular pathology (56.86 %), arterial hypertension (89.66 %); ENT diseases were less common – 41.18 % (nasal allergy – 80.96 %, deep-rooted rhinosinusitis polyposa – 9.52 %, combination of nasal allergy and deep-rooted rhinosinusitis polyposa; pathology of endocrine system (25.49 %), of which the most common was diabetes mellitus types 1 and 2 (76.92 %) took third place (see Fig. 1).

The median level of peripheral blood eosinophils in patients in the first group was 280 [190; 358] cells per μl, in the second – 250 [135; 380], in the comparison group – 140 [95; 140]. The median level of peripheral blood neutrophils in patients in the first group was 5.6 [3.98; 6.475] (109/l), in the second – 4.8 [4.1; 5.65] (109/l), in the comparison group – 3.1 [2.5; 3.56] (109/l). Statistically significantly higher levels of peripheral blood eosinophils and neutrophils were found in patients with asthma combined with obesity compared to obese patients without asthma ($p < 0.001$). The statistically significant differences identified highlight the contribution of these cells to inflammatory processes in BA.

The median CRP hs level in the first group was 4.23 [4.04; 4.63] mg/l, in the second – 5.4 [4.9; 6.1], in the comparison group – 3.4 [3.1; 3.67]. In three groups, the values of CRP hs increased significantly and were maximum in patients with severe bronchial asthma ($p < 0.001$). The level of other laboratory parameters among the subjects was comparable ($p > 0.05$).

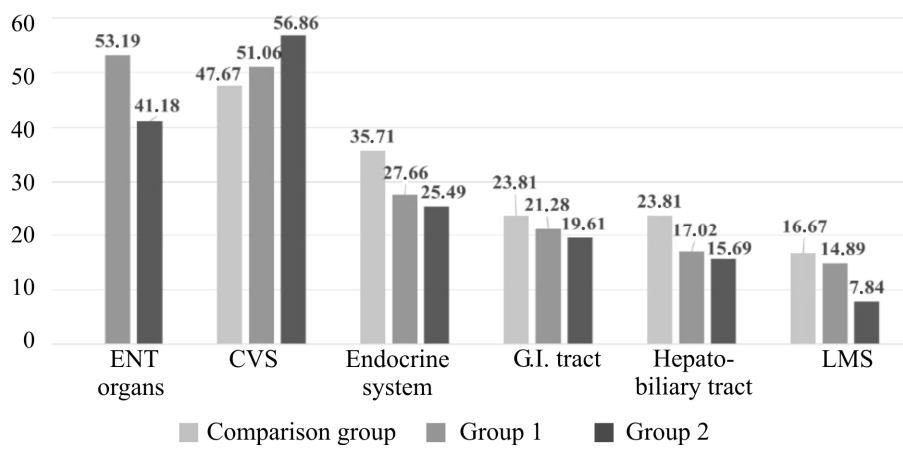


*Fig. 1. Spectrum of concomitant pathology in the study groups*

The median level of total IgE for patients in group 1 was 140.1 [107.65; 242.25] IU/ml, in group 2 – 135.2 [112.75; 310.45], and for the comparison group – 18.25 [10.1; 32.1]. There were no statistically significant differences in total IgE levels between patients with asthma and obesity ($p = 1.0$). There were no statistically significant differences in the presence and spectrum of sensitization between patients in groups 1 and 2 ($p > 0.05$).

In patients of the 1st group and the comparison group, the results of spirometry did not reveal any disturbances in the mechanical properties of the external respiratory apparatus. Spirometry values for all subjects are shown before the bronchodilator test (Fig. 2). In subjects with severe asthma combined with obesity, the FVC index was within the normal range, while the FEV1 and FEV1/FVC levels were below normal values, indicating more pronounced obstruction in patients with severe asthma combined with obesity. Analysis of the parameters of external respiration function in all study groups showed significant differences in such parameters as FVC ($p < 0.001$), FEV1 ($p < 0.001$) and FEV1 / FVC ($p < 0.001$), with lower values of these indicators in patients with severe asthma combined with obesity.

The analysis of the level of asthma control in the groups was based on the AST test results. The median AST test result in patients of the 1st group was 21 [19; 24] points and was significantly higher ($p < 0.001$) than the median AST test in patients of the 2nd group – 16 [10.5; 21] points.

In severe cases of asthma combined with obesity, patients were more likely to have uncontrolled disease – 58.8 %, while in mild cases of asthma combined with obesity, patients had partial control – 46.8 %. In patients with TBA combined with obesity, an uncontrolled course of the disease was more common ($p = 0.008$) and less common in control ($p = 0.009$), compared with subjects with a mild course of BA combined

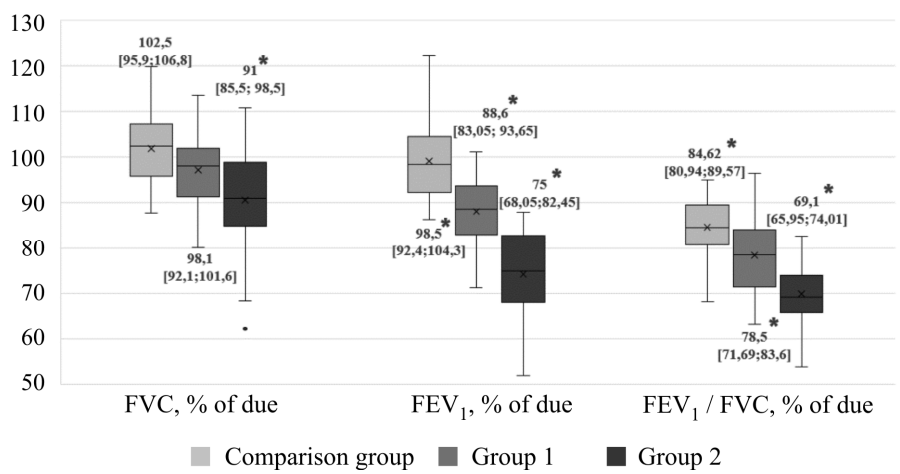


*Fig. 2. Main indicators of spirometry in patients of all study groups.*
*Note: * – significance of differences when comparing groups pairwise using the Kruskal – Wallis test with Bonferroni correction for multiple comparisons*

with obesity. A moderate-strength relationship was observed between the compared features (V = 0.326).

The study analyzed the spectrum of cytokines in patients of all groups (Fig. 3). The association of asthma with obesity, regardless of severity, was characterized by an increase in plasma levels of TNF-α, IFN-γ, IL-6, IL-17, IL-4 ($p < 0.05$). Statistically significantly higher levels of cytokines TNF-α, IFN-γ, IL-6, IL-17 and the lowest level of IL-10 were found in patients with severe asthma combined with obesity, compared to subjects with mild asthma combined with obesity ($p < 0.001$) and only obesity without asthma ($p \leq 0.001$). This may indicate an additional contribution of adipose tissue to "low-intensity inflammation" and the severity of asthma in this category of patients.

All patients underwent analysis of serum intestinal endotoxin and fecal zonulin levels. Statistically significantly higher values of the median level of intestinal intestinal endotoxin in blood serum – 2.1 [1.85; 2.23] EU/ml and fecal zonulin – 93 [83.45; 96] ng/ml were obtained in patients with severe bronchial asthma combined with obesity ($p < 0.001$). Kim and Baioumy also observed increased zonulin levels in patients with severe asthma in their studies [8; 9].

In a number of studies, the same trend was observed with endotoxemia, which increased with the severity of the course of bronchial asthma [10; 11]. Higher concentrations of ET in patients with severe bronchial asthma may be associated with increased shunt circulation due to frequent use of SABA against the background of uncontrolled bronchial asthma [12].

In patients of the 2nd group, a correlation analysis was performed of the level of fecal zonulin and intestinal ET with the main clinical, laboratory and instrumental indicators, markers of systemic inflammation. The level of fecal zonulin was positively correlated with the level of intestinal ET in patients with severe BA combined with obesity ($p < 0.001$; $rs = 0.813$).

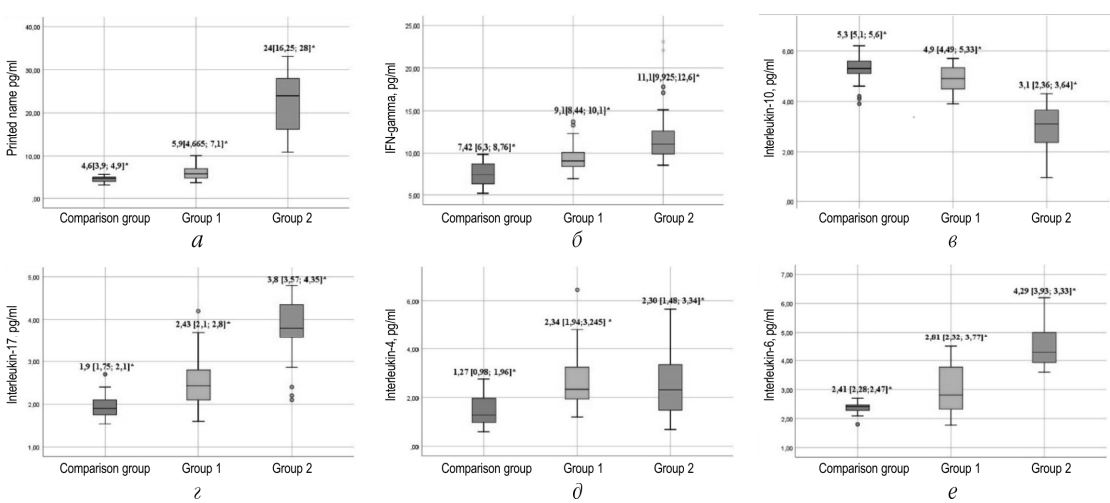


*Fig. 3. The level of cytokines in peripheral blood in patients of all study groups (a–e).*
*Note: p* – significance of differences when comparing groups pairwise using the Kruskal-Wallis test with Bonferroni correction for multiple comparisons*

The identified correlation had a high strength of connection according to the Chaddock scale. It is known that in patients with obesity, the intestinal microbial composition changes with a shift towards gram-negative bacteria, which can lead to an increase in the level of intestinal ET [13], an increase in proinflammatory cytokines and ultimately contribute to increased intestinal permeability with an increase in the level of fecal zonulin [14]. When assessing the correlation relationships between fecal zonulin and intestinal ET with anthropometric parameters in patients of group 2, statistically significant direct correlations were established with BMI (zonulin – $p < 0.001$, $rs = 0.820$; ET – $p < 0.001$, $rs = 0.888$), WC (zonulin – $p < 0.001$, $rs = 0.508$; ET – $p < 0.001$, $rs = 0.615$), HC (zonulin – $p = 0.001$, $rs = 0.446$; ET – $p < 0.001$, $rs = 0.498$), WC/HC ratio (zonulin – $p = 0.046$, $rs = 0.281$; ET – $p = 0.005$, $rs = 0.385$). In studies by Moreno-Navarrete [15] and Mörkl [16], positive correlations of zonulin levels with anthropometric parameters in obese patients were also observed. Negative statistically significant associations were found between the levels of fecal zonulin and intestinal endotoxin with FEV1 (zonulin – $p < 0.001$, $rs = -0.576$; ET – $p = 0.002$, $rs = -0.418$), AST test results (zonulin – $p < 0.001$, $rs = -0.704$; ET – $p < 0.001$, $rs = -0.551$) and a positive correlation with the lack of disease control (zonulin – $p < 0.001$, $rs = 0.550$; ET – $p < 0.001$, $rs = 0.302$), a negative correlation was also found between the level of zonulin and FVC ($p = 0.017$; $rs = -0.334$) in patients with severe asthma combined with obesity. In patients of the 2nd group with an increase in the level of fecal zonulin and intestinal ET, an increase in the level of hs-CRP (zonulin – $p < 0.001$, $rs = 0.628$; ET – $p < 0.001$, $rs = 0.533$), TNF-α (zonulin – $p < 0.001$, $rs = 0.594$; ET – $p = 0.002$, $rs = 0.433$), IL-6 (zonulin – $p < 0.001$, $rs = 0.645$; ET – $p < 0.001$, $rs = 0.841$), IL-17 (zonulin – $p < 0.001$, $rs = 0.532$; ET – $p = 0.009$, $rs = 0.363$), IFN-γ (zonulin – $p < 0.001$, $rs = 0.516$; intestinal ET – $p = 0.037$, $rs = 0.292$) and a decrease in the level of IL-10 (zonulin – $p < 0.001$, $rs = -0.556$; ET – $p = 0.001$, $rs = -0.439$). The correlations found ranged from weak to strong according to the Chaddock scale. Other studies have also found positive correlations of zonulin levels with IL-6 [15; 16], CRP [16], TNF-α [17]. The release of proinflammatory cytokines by adipose tissue may begin in response to an increase in circulating ET levels [18]. Выявленные корреляции имели от слабой до высокой тесноту связи по шкале Чеддока. В других исследованиях также были выявлены положительные корреляции уровня зонулина с IL-6 [15; 16], СРБ [16], TNF-α [17]. According to previous studies, the level of zonulin [15] and intestinal ET [19] positively correlated with LDL (zonulin – $p < 0.001$, $rs = 0.674$; ET – $p < 0.001$, $rs = 0.734$) and negatively with HDL (zonulin – $p < 0.001$, $rs = -0.537$; ET – $p < 0.001$, $rs = -0.591$), which was also revealed in our study. When the level of ET increases, it is likely that it is deposited in the "HDL+ET" complex (LDL is represented in the blood circulation) [12]. A study by Zhang et al. suggested that zonulin increases adipose tissue via the endocannabinoid pathway by increasing intestinal wall permeability and subsequently developing dyslipidemia [20].

## Conclusions

Severe bronchial asthma (BA) in combination with obesity is characterized by certain features – later onset, lack of BA control in most patients, significantly lower FVC, FEV1, FEV1 / FVC, standard sensitization profile, higher levels of proinflammatory cytokines (TNF-α, IL-6, IFN-γ, IL-17), CRP, fecal zonulin, intestinal ET, low IL-10 levels. The most common concomitant disease in this group of patients was arterial hypertension. In patients with severe asthma combined with obesity, positive correlations were obtained between the levels of fecal zonulin and intestinal ET, indicating a relationship between these two indicators.

When conducting a correlation analysis in this group of patients with an increase in the level of fecal zonulin and intestinal ET, an increase in the level of CRPhs, TNF-α, IL-6, IFN-γ, IL-17, BMI, WC, HC, WC/HC, LDL, an increase in the frequency of uncontrolled asthma and a decrease in the level of IL-10, FEV1, AST test, HDL were observed. The obtained results allow us to speak about the existence of a clinical complex "severe bronchial asthma – obesity – intestinal endotoxemia and increased intestinal permeability", which is formed through the "intestine – lung" axis and is characterized by the predominance of proinflammatory markers, increased intestinal ET and fecal zonulin levels, and reduced external respiratory function.

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