BIOCHEMISTRY

THE ROLE OF FATTY ACIDS AND LIPID INFLAMMATORY MEDIATORS IN THE DEVELOPMENT OF SMALL AIRWAY DYSFUNCTION IN ASTHMA COMPLICATED WITH OBESITY

Yurenko A.V.,
Novgorodtseva T.P.,
Denisenko Yu.K.,
Antonyuk M.V.,
Mineeva E.E.

Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment (Russkaya str., 73G, Vladivostok 690105, Russian Federation)

Corresponding author:
Alla V. Yurenko,
e-mail: yurenko_alla@mail.ru

ABSTRACT

Background. *Small airway involvement is important in determining the phenotypes of bronchial asthma. Establishing the mechanisms of dysfunction of small airways will make it possible to predict the course and control bronchial asthma.*

The aim. *To study the association between the modification of the composition of fatty acids, lipid inflammatory mediators (eicosanoids, plasmalogens) and the functional state of small airways and to identify lipid biomarkers for the development of small airway dysfunction in bronchial asthma associated with obesity.*

Materials and methods. *The study included 85 patients with mild, partially controlled asthma. Of these, 39 patients with normal body weight (Group 1) and 46 patients with grade I–II obesity (Group 2). The control group consisted of 30 healthy volunteers. The function of the small airways was assessed according to spirometry and body plethysmography. The composition of fatty acids and plasmalogens in blood plasma was assessed by gas chromatography-mass spectrometry. In the blood serum, the content of thromboxane B2 and leukotriene B4was determined. Statistical processing was performed using the Statistica 6.1 program (StatSoft Inc., USA). Interrelations between pairs of traits were examined using the Spearman correlation test (r). Differences were considered statistically significant at $p < 0.05$.*

Results. *In the combined course of asthma and obesity, dysfunction of the small airways develops against the background of generalized bronchial obstruction. A modification of lipid metabolism was revealed, manifested by an increase in the levels of saturated, monoenoic, n-6 polyunsaturated fatty acids against the background of a deficiency of n-3 polyunsaturated fatty acids and phospholipids with an alkenyl bond – plasmalogens. It has been shown that bronchial asthma, aggravated by obesity, occurs against the background of increased synthesis of inflammatory lipid mediators – eicosanoids (thromboxane B_2 and leukotriene B_4). Evaluation of the correlations between the studied lipids and the function of small airways revealed a high degree of relationship between their elements.*

Conclusion. *An important pathogenetic link in the formation of small airway dysfunction in bronchial asthma aggravated by obesity is a violation of fatty acid metabolism and plasmalogen synthesis, an increase in the formation of inflammatory lipid mediators.*

Key words: *bronchial asthma, small airways, fatty acids, plasmalogens*

Received: 20.07.2022
Accepted: 02.03.2023
Published: 05.05.2023

For citation: Yurenko A.V., Novgorodtseva T.P., Denisenko Yu.K., Antonyuk M.V., Mineeva E.E. The role of fatty acids and lipid inflammatory mediators in the development of small airway dysfunction in asthma complicated with obesity. *Acta biomedica scientifica*. 2023; 8(2): 50-64. doi: 10.29413/ABS.2023-8.2.6

РОЛЬ ЖИРНЫХ КИСЛОТ И ЛИПИДНЫХ ВОСПАЛИТЕЛЬНЫХ МЕДИАТОРОВ В РАЗВИТИИ ДИСФУНКЦИИ МАЛЫХ ДЫХАТЕЛЬНЫХ ПУТЕЙ ПРИ БРОНХИАЛЬНОЙ АСТМЕ, АССОЦИИРОВАННОЙ С ОЖИРЕНИЕМ

Юренко А.В.,
Новгородцева Т.П.,
Денисенко Ю.К.,
Антонюк М.В.,
Минеева Е.Е.

Владивостокский филиал
ФГБНУ «Дальневосточный научный центр физиологии и патологии дыхания» – Научно-исследовательский институт медицинской климатологии и восстановительного лечения (690105, Россия, г. Владивосток, ул. Русская, 73г)

Автор, ответственный за переписку:
Юренко Алла Валентиновна,
e-mail: yurenko_alla@mail.ru

РЕЗЮМЕ

Обоснование. *Поражение малых дыхательных путей (МДП) имеет большое значение в определении фенотипов бронхиальной астмы (БА). Установление механизмов дисфункции МДП позволит прогнозировать течение и контролировать БА.*

Цель исследования. *Изучить взаимосвязь модификации состава жирных кислот, липидных воспалительных медиаторов (эйкозаноиды, плазмалогены) с функциональным состоянием малых дыхательных путей и выделить липидные биомаркеры развития дисфункции МДП при БА, ассоциированной с ожирением.*

Материалы и методы. *В исследование включено 85 пациентов с лёгкой частично контролируемой БА. Из них 39 пациентов с нормальной массой тела (1-я группа) и 46 пациентов с ожирением 1–2-й степени (2-я группа). Группу контроля составили 30 здоровых добровольцев. Функцию МДП оценивали по данным спирометрии, бодиплетизмографии. Состав жирных кислот (ЖК) и плазмалогенов в плазме крови оценивали методами газовой хромато-масс-спектрометрии. В сыворотке крови определяли содержание тромбоксана B_2 ($ТХВ_2$) и лейкотриена B_4 ($ЛТВ_4$). Статистическую обработку осуществляли с использованием программы Statistica 6.1 (StatSoft Inc., США). Взаимосвязи между парами признаков исследовали с использованием критерия корреляции Спирмена (r). Различия считали статистически значимыми при $p < 0,05$.*

Результаты. *При сочетанном течении БА и ожирения развивается дисфункция МДП на фоне генерализованной бронхиальной обструкции. Выявлено нарушение метаболизма липидов, проявляющееся повышением уровней насыщенных, моноеновых, n-6 полиненасыщенных ЖК на фоне дефицита n-3 полиненасыщенных ЖК и фосфолипидов с алкенильной связью – плазмалогенов. Показано, что БА, отягощённая ожирением, протекает на фоне повышенного синтеза воспалительных липидных медиаторов – эйкозаноидов ($ТХВ_2$, $ЛТВ_4$). Оценка корреляционных взаимосвязей изучаемых липидов и функции МДП выявила высокую степень взаимоотношений между их участниками.*

Заключение*. Важным патогенетическим звеном формирования дисфункции МДП при БА, отягощённой ожирением, является нарушение метаболизма жирных кислот и синтеза плазмалогенов, увеличение образования воспалительных липидных медиаторов.*

Ключевые слова: *бронхиальная астма, малые дыхательные пути, жирные кислоты, плазмалогены*

Статья поступила: 20.07.2022
Статья принята: 02.03.2023
Статья опубликована: 05.05.2023

Для цитирования: Юренко А.В., Новгородцева Т.П., Денисенко Ю.К., Антонюк М.В., Минеева Е.Е. Роль жирных кислот и липидных воспалительных медиаторов в развитии дисфункции малых дыхательных путей при бронхиальной астме, ассоциированной с ожирением. *Acta biomedica scientifica*. 2023; 8(2): 50-64. doi: 10.29413/ABS.2023-8.2.6

OBJECTIVES

Bronchial asthma (BA) is still one of the topical problems in medicine. Chronic inflammation of the airways leads to the development of reversible bronchial obstruction. Mechanisms study leading to functional disorders of the respiratory system and the development of various phenotypes of bronchial asthma, including BA complicated with obesity abdominal obesity (AO), remains relevant. A significant role in the development of this phenotype of bronchial asthma is attributed not only to immune, but also to hormonal disorders specific to obesity [1, 2]. In recent years, the role of small airways in the pathogenesis of BA has paid much attention [3, 4]. Small airway dysfunction has an unfavorable effect on the clinical manifestations of the disease, predetermining uncontrolled course, and statistically significantly increases the risks of BA acute conditions [5]. In the vast majority of cases, small airway dysfunction is present in any degree of asthma severity; at the same time, the changes are diagnosed not only against the background of mild generalized bronchial obstruction, but also with normal pulmonary function [6]. The pathophysiologic mechanisms of small airway dysfunction development in BA are under active research, the results of which are contradictory due to the heterogeneity of pathogenesis and clinical manifestations of asthma [7].

Fatty acids (FAs) with their important structural, energetic and signaling functions play a key role in the pathogenesis of bronchopulmonary diseases, as well as in the development of abdominal obesity. Lipids are extremely diverse in terms of their chemical structure and the functions they perform. For example, phospholipids (PLs) and their constituent polyunsaturated fatty acids (PUFAs) are the main components of pulmonary surfactant. Modification of PUFA composition and alteration of surfactant PL molecular species may influence the development of bronchial asthma [8]. Lipid metabolism disorder in AO plays no less significant role [9].

PLs are subdivided into several subclasses of ether lipids – diacyl, alkyl (alkenyl)-acyl, or plasmalogens. The link of disorders in plasmalogens biosynthesis with the development of respiratory diseases and abdominal obesity has been established. This has prompted interest in them as promising therapeutic targets. The presence of plasmalogens in cell membranes affects the properties and functions of membranes and their receptors. Plasmalogens of surfactant play a protective role due to antioxidant activity [10]. The peculiarity of phospholipids and, above all, plasmalogens of cell membranes is that they are carriers of precursors of the most important secondary messengers, such as leukotrienes, prostaglandins, platelet-activating factor (PAF) and some others [11]. Since plasmalogens constitute a large fraction of total lipids in humans, changes in their levels have been shown to affect membrane properties and therefore signaling pathways involved in the inflammatory cascade [12]. The available sporadic data on impaired synthesis of plasmalogens in obstructive lung diseases give grounds to consider these compounds as essential participants in the pathogenesis of bronchopulmonary diseases [13].

Lipid mediators, including derivatives of ω-3 and ω-6 PUFAs – eicosanoids (leukotrienes, thromboxanes), docosanoids, and pro-resolving lipid mediators – play an active role in the development of chronic airway inflammation [14]. Initiation of inflammation in BA is mainly due to the participation of oxidized derivatives of arachidonic acid (ARA); at the same time, oxidized derivatives of docosahexaenoic acid (DHA), dominant in the 2nd position of plasmalogous forms of phospholipids, are assigned the role of a proinflammatory mediator [15]. Fatty acid metabolism and plasmalogens synthesis disorder, increased formation of proinflammatory derivatives is one of the reasons for the aggravation of the course of BA, an important factor in the formation of chronic inflammation in BA and AO [16].

Thus, polyunsaturated fatty acid, plasmalogens are important structural and signaling molecules involved in both the regulation of chronic inflammation and bronchoconstriction. Lipids polyfunctionality, the presence of common etiologic and pathogenetic mechanisms of bronchial asthma and obesity formation determine the special significance of studying the participation of individual lipid classes in the development of systemic inflammation and small airway dysfunction in BA associated with obesity. Determining the role of lipid mediators of inflammation in the formation of disorders of external respiratory function in patients with bronchial asthma will allow to identify therapeutic targets for improving disease control.

THE AIM OF THE STUDY

To study the interrelation of modification of fatty acid composition, lipid inflammatory mediators (eicosanoids, plasmalogens) with the functional state of small airways and to identify lipid biomarkers of the development of small airway dysfunction in bronchial asthma associated with obesity.

MATERIALS AND METHODS

The study was conducted in accordance with the requirements of the WMA Declaration of Helsinki (revision 2013), with the approval of the local ethical committee of the Vladivostok branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment (minutes No. 8 of 28.06.2022) and under the conditions of voluntary informed consent of all included patients and volunteers.

Study design. The study was performed as a prospective single-center randomized study.

It included patients who were on examination and treatment in the clinical department of the Vladivostok

branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment from 2019 to 2021.

Inclusion criteria: patients with mild, partially controlled bronchial asthma, with normal body weight (NBW) and abdominal obesity of grade I–II, aged from 20 to 65 years.

Exclusion criteria: patients with moderate and severe bronchial asthma of uncontrolled course, with chronic obstructive pulmonary disease, occupational diseases of bronchopulmonary system, abdominal obesity of grade III and IV, endocrine diseases and other diseases of internal organs in decompensation stage.

Eighty-five patients with mild, partially controlled bronchial asthma, including 31 men and 64 women, aged 20–65 years (mean age 50.72 ± 15.24 years) were investigated. Patients were divided into two groups based on the Body Mass Index (BMI, Quetelet's index). Group 1 included 39 patients with BA and normal body weight (BMI = 23.32 ± 2.47 kg/m^2), and Group 2 included 46 patients with BA and AO of grade I and II (BMI = 34.06 ± 3.48 kg/m^2). The control group consisted of 30 conditionally healthy volunteers. The groups were comparable in terms of sex and age.

Clinical, laboratory and functional examination of patients was carried out in accordance with the standards of examination of patients with BA and obesity. BA diagnosis was made according to the international consensus criteria for the diagnosis and treatment of bronchial asthma (GINA, 2021). BA history duration was up to 5 years in 49 % of cases and more than 5 years in 51 % of cases. All patients with bronchial asthma received baseline therapy with a fixed combination of a low-dose inhaled glucocorticosteroid (budesonide – 200–400 μg/day) and a long-acting β2-agonist (formoterol) (GINA, 2021; national asthma guidelines). The ACQ-5 (Asthma Control Questionnaire) test was used to assess the level of disease control. ACQ-5 test scores between 0.75 and 1.5 indicated partial control of the disease [17]. To diagnose alimentary-constitutional obesity, the World Health Organization recommendations were followed [18].

Pulmonary function tests (PFTs) were performed using Master Screen Body apparatus (Germany). According to spirometry data, the vital capacity (VC%), expiratory reserve volume (ERV), forced vital capacity (FVC%), forced expiratory volume in 1 second (FEV_1%), the ratio of FEV_1 to VC (FEV_1/VC%), the ratio of FEV_1 to FVC (FEV_1/FVC%), peak expiratory flow rate after exhalation of 25 % FVC ($PEFR_{75}$ %), maximal expiratory flow at 25 % of FVC (MEF_{75}), maximal expiratory flow at 50 % of FVC (MEF_{50}), maximal expiratory flow at 75 % of FVC (MEF_{25}), and maximal mid-expiratory flow ($MMEF_{25–75}$) were estimated in % of the target parameters. To investigate bronchodilator reversibility, a sample with salbutamol (400 μg) was used [19].

Static lung volumes and capacities were assessed by body plethysmography in % of target values: functional residual capacity (FRCplet); residual volume (RV); total lung capacity (TLC); percentage ratio of RV/TLC; airway resistance on inhalation (inhalation resistance) and exhalation (exhalation resistance); total airway (bronchial) resistance (Rtot).

Blood plasma lipids were extracted according to the method of Bligh and Dyer (Bligh and Dyer, 1959). The levels of fatty acids (FAs) and plasmalogens were estimated by the content of FA methyl esters (FAME) and plasmalogen derivatives, dimethyl acetals (DMA), which were determined by gas chromatography-mass spectrometry. The ratio of the plasmalogen level to the corresponding fatty acid methyl ester in terms of the number of carbon atoms was calculated. Fatty acid methyl esters and dimethylacetals were prepared according to the method of Carreau and Duback (1978). FAME peaks identification was done by retention times of individual fatty acid esters and by equivalent chain length values (Christie, 1988). DMAs were identified by comparing their retention times with those of the 16:0DMA and 18:0DMA standards.

The content of eicosanoids was determined by the amount of their stable metabolites in serum – thromboxane B_2 and leukotriene B_4. Minicolumns (Minicolumns for Sample Preparation, USA) were used for sample preparation. Quantitative level of thromboxane B_2 and leukotriene B_4 was determined by immunoenzyme technique using ELISA kits of Enzo Life Sciences (USA). Measurement was performed in flat-bottom 96-well plates on a spectrophotometer (Biotek Power Wave, USA).

Statistical processing of data was performed using the standard statistical software package Statistica 6.1 for Windows (StatSoft Inc., USA). Hypothesis tests for the normal distribution of quantitative signs in groups were performed using Kolmogorov – Smirnov, Shapiro – Wilk and Pearson's chi-squared tests (χ^2). Descriptive statistics are presented in the text as M ± SD (in case of normal distribution of the trait), where M is the mean, SD is the standard deviation, and Me (L_q; U_q) (in case of non-normal distribution of the trait), where Me is the median, L_q is the lower quartile, and U_q is the upper quartile. Statistically significant difference between alternative quantitative parameters with a distribution corresponding to the normal distribution law was assessed using Student's t-test, otherwise using two-samples Wilcoxon test, Mann – Whitney U test, and Kolmogorov – Smirnov test. The interrelation between pairs of traits was investigated using the Spearman's rank correlation coefficient (r). Differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

Clinical and functional characteristics of the examined patients are presented in Table 1. Pulmonary function indicators according to spirometry in patients with mild BA and NBW (Group 1) were reduced than in control group: expiratory reserve volume % – by 30 % ($p = 0.035$); FEV_1/VC% – by 7 % ($p = 0.008$); FEV_1/FVC% – by 7% ($p = 0.015$); MEF_{75}% – by 26 % ($p = 0.003$); MEF_{50}% – by 29 % ($p = 0.003$); MEF_{25}% – by 27 % ($p = 0.003$); $MMEF_{25–75}$% – by 28 % ($p = 0.009$).

TABLE 1

CLINICAL AND FUNCTIONAL CHARACTERISTICS OF THE EXAMINED PATIENTS

Indicators	Control group (n = 30)	Group 1: BA + IBW (n = 39)	Group 2: BA + AO (n = 46)	Statistical significance level (p)
Age	35.88 ± 8.23	45.86 ± 16.95	59.83 ± 11.6	–
Body mass index, kg/m^2	23.51 ± 2.91	24.55 ± 3.27	34.06 ± 3.48	$p_{c-2} < 0.001$; $p_{1-2} < 0.001$
ACQ test, scores	–	0.9 (0.6; 1.2)	1 (0.5; 1.6)	–
VC, %	105.65 (98.28; 121.7)	107.15 (103.18; 119.1)	107.4 (96; 126.45)	–
IC, %	108.75 (86.18; 115.48)	112.4 (103.7; 127.2)	127.05 (101.8; 146.98)	–
ERV, %	124.64 (108.38; 139.35)	87.21 (76.91; 101.22)	58.71 (50.23; 93.23)	$p_{c-1} = 0.035$ $p_{c-2} < 0.001$ $p_{1-2} = 0.013$
FVC, %	105.51 (99.73; 123)	107.25 (103.91; 114.38)	107 (85.00; 114.51)	–
FEV_1, % of target	104.42 (95.68; 112.01)	94.85 (90.88; 105.55)	85.11 (76.65; 105.81)	$p_{c-2} = 0.004$;
FEV_1/VC, %	74.82 (71.25; 82.85)	69.78 (64.79; 73.83)	64.91 (58.44; 70.99)	$p_{c-2} < 0.001$ $p_{c-1} = 0.008$
FEV_1/FVC, %	78.72 (73.89; 84.38)	73.45 (70.26; 77.06)	70.27 (62.21; 76.25)	$p_{c-1} = 0.015$ $p_{c-2} = 0.002$;
MEF_{75}, %	100.45 (84.08; 117.71)	74.51 (60.03; 84.89)	63.41 (37.55; 87.91)	$p_{c-1} < 0.001$ $p_{c-2} = 0.003$
MEF_{50}, %	82.85 (64.83; 110.43)	59.20 (3.31; 70.05)	42.6 (8.55; 58.05)	$p_{c-1} = 0.003$ $p_{c-2} < 0.001$ $p_{1-2} = 0.039$
MEF_{25}, %	49.15 (41.18; 90.13)	35.65 (26.28; 48.45)	26.5 (23.9; 36.1)	$p_{c-1} = 0.009$ $p_{c-2} < 0.001$
$MMEFR_{25-75}$, %	73.75 (57.55; 97.05)	53.35 (37.18; 59.45)	33 (21.75; 50.4)	$p_{c-1} = 0.001$ $p_{1-3} < 0.001$ $p_{2-3} = 0.042$
Rin, kPa × s/l	0.17 (0.14; 0.2)	0.26 (0.2; 0.33)	0.32 (0.26; 0.38) 23%?	$p_{c-1} = 0.041$ $p_{c-2} = 0.007$
Rex, kPa × s/l	0.22 (0.15; 0.3)	0.38 (0.28; 0.41)	0.4 (0.34; 0.66)	$p_{1-2} = 0.041$ $p_{c-2} = 0.003$ $p_{c-1} = 0.017$
Rtot, kPa × s/l	0.19 (0.14 0.25)	0.31 (0.2; 0.35)	0.36 (0.28; 0.51)	$p_{c-1} = 0.017$ $p_{c-2} < 0.001$ $p_{1-2} = 0.025$
FRC_{plet}, %	100.4 (92.23; 115.2)	106 (96.15; 122.03)	113.5 (103.03; 125.4)	–
RV, %	107.85 (92.68; 118.53)	109.9 (93.15; 143.25)	114.05 (105.1; 139.3)	$p_{c-2} = 0.037$
TLC, %	96.5 (92.6; 115.73)	106,45 (104,63; 111,65)	107.6 (96.75; 115.55)	–
RV/TLC, %	98.15 (91.13; 100.5)	105.4 (94.75; 122.05)	102.6 (93.42; 127.32)	–

Note. Descriptive statistics are presented as M ± SD, where M – mean, SD – standard deviation (in case of normal distribution of the trait); in case of distribution not corresponding to normal distribution – as Me (L_q; U_q), where Me – median, L_q – lower quartile, U_q – upper quartile; IC – inspiratory capacity; ERV – expiratory reserve volume; p_{c-1} – statistical significance of differences between the control group and group 1; p_{c-2} – statistical significance of differences between the control group and group 2; p_{1-2} – statistical significance of differences between Groups 1 and 2. Values are given for $p < 0.05$ only.

The body plethysmography data revealed an increase in inhalation resistance by 53 % ($p = 0.041$) and exhalation resistance by 71 % ($p = 0.017$), total inhalation and exhalation resistance by 63 % ($p = 0.017$), which is specific for bronchial obstruction.

Patients with bronchial asthma and abdominal obesity (group 2) had more pronounced changes in PFT parameters than in the control group. A 53 % decrease in expiratory reserve volume % ($p < 0.001$), 18 % decrease in FEV_1 % ($p = 0.004$), 13 % decrease in FEV_1/VC% % ($p < 0.001$), 11 % decrease in FEV_1/FVC% ($p = 0.002$), 37 % decrease in MEF_{75}% ($p < 0.001$), 48 % decrease in MEF_{50} % ($p < 0.001$), 46 % decrease in MEF_{25}% ($p < 0.001$), 55 % decrease in $MMEF_{25–75}$% ($p < 0.001$) were noted. Body plethysmography revealed an increase in inhalation resistance by 88 % ($p = 0.007$) and exhalation resistance by 82 % ($p = 0.003$), total inhalation and exhalation resistance by 89 % ($p < 0.001$), and RV by 6 % ($p = 0.037$).

Comparative analysis of PFT parameters in patients of Groups 1 and 2 revealed statistically significant differences. For example, patients with bronchial asthma combined with obesity compared to patients with IBW showed a 32 % decrease in expiratory reserve volume ($p = 0.013$), a 28 % decrease in MEF_{50} ($p = 0.039$), a 38 % decrease in $MMEF_{25–75}$ ($p = 0.041$), and a 16 % increase in total inhalation and exhalation resistance ($p = 0.025$).

The data obtained indicate the progression of generalized bronchial obstruction, including at the level of small bronchi in obesity-associated BA.

The result of composition of individual fatty acids and plasmalogens are summarized in Table 2. Comparative analysis of FA plasma composition between patients with BA and NBW (Group 1) and the control group showed a statistically significant increase in the proportion of myristic acid (14:0) by 33 % ($p = 0.044$) and a decrease in digomo-γ-linolenic acid (20:3ω-6) by 27 % ($p = 0.036$).

A statistically significant increase in the proportion of myristic acid (14:0) more than 2-fold ($p < 0.001$) was observed in patient Group 2 with BA in combination with AO compared to controls. Along with the increase in saturated fatty acids (SFAs), the content of some monoenoic acids (MFAs) increased, in particular palmitoleic acid (16:1ω-7) by 28 % ($p < 0.001$), hexadecenoic acid (16:1ω-9) by 21 % ($p < 0.001$) and heptadecenoic acid (17:1) by 40 % ($p < 0.001$).

Modification of PUFA of blood plasma in patient Group 2 was characterized by statistically significant decrease of: eicosapentaenoic acid (20:5ω-3) – by 38 % ($p = 0.012$), and docosahexaenoic acid (22:6ω-3) – by 34 % ($p = 0.012$) in comparison with the control group. There was a trend of 16 % decrease in docosapentaenoic (22:5ω-3) acid. Against this background, an increase in the proportion of α-linolenic (18:3ω-3) acid by 37 % ($p < 0.001$) versus to the control was observed.

Modification of ω-6 PUFA composition was observed: an increase in the levels of γ-linolenic (18:3ω-6) acid by 33 % ($p = 0.015$) and digomo-γ-linolenic (20:3ω-6) by 7 %, and a decrease in adrenic acid (22:4ω-6) by 29 % ($p < 0.001$).

When comparing the parameters of FA composition between the Groups 1 and 2 in BA patients with obesity, an increase in the proportion of saturated fatty acids was found: myristic acid (14:0) – by 62 % ($p = 0.035$), stearic acid (18:0) – by 10 %. The content of MFAs, palmitoleic acid (16:1ω-7) and hexadecenoic acid (16:1ω-9), also increased by 23 % ($p = 0.004$) and 34 % ($p = 0.005$), respectively.

In the comparative analysis between Groups 1 and 2, statistically significant differences in the composition of PUFAs of the ω-3 family were determined. So, in patients of Group 2 the level of eicosapentaenoic FA (20:5ω-3) was lower by 34 % ($p = 0.017$), docosahexaenoic FA (22:6ω-3) – by 35 % ($p = 0.035$) relative to the indicators in Group 1. In addition, the level of α-linolenic (18:3ω-3) acid in Group 2 patients was 36 % higher ($p = 0.038$) than in Group 1.

A modification in the composition of PUFAs of the ω-6 family was identified, which was manifested by an increase in the proportion of γ-linolenic acid (18:3n6) and digomo-γ-linolenic acid (20:3ω-6) by 43 % ($p = 0.015$) and 46 % ($p = 0.042$), respectively, and a decrease the level of adrenic acid (22:4ω-6) by 33 % ($p < 0.001$). The content of arachidonic acid (20:4ω-6) in patients in both groups has no statistically significantly differences. However, the decrease in the proportion of 20:5ω-3 PUFA in Group 2 resulted in an increase in the 20:4ω-6/20:5ω-3 ratio, the value of which was 30 % higher compared to Group 1 ($p = 0.017$) and 15 % higher versus to controls ($p = 0.042$). A disbalance of ω-3 and ω-6 PUFAs with accumulation of ω-6 PUFAs leads to preferential synthesis of their pro-inflammatory metabolites.

In Group 1 (BA and NBW) no statistically significant changes in plasma plasmalogens content were found (Table 2). Group 2 (BA with obesity) showed a decrease in plasmalogens DMA16:0 and DMA18:0. Indeed, DMA16:0 and DMA18:0 levels decreased by 31 % ($p = 0.002$) and 32 % ($p = 0.028$) than in controls and by 41 % ($p < 0.001$) and 34 % ($p = 0.036$) than in Group 1, respectively. The ratio of all DMA16:0 to total palmitic acid in blood (DMA16:0/FAME16:0) decreased by 30.9 % ($p = 0.002$) versus to control and by 85 % ($p < 0.001$) compared to Group 1. The index level of the relative content of all DMA18:0 to total blood stearic acid (DMA18:0/FAME18:0) decreased by 31.8 % ($p = 0.002$) and 25 % ($p < 0.001$) versus to the control group and Group 1 respectively. There were no statistically significant differences in DMA18:1 and DMA20:0 levels between the healthy and BA patient groups.

Thus, the results of this study showed decreased levels of alkenyl-linked phospholipids during the development of AO-associated BA.

The content of pro-inflammatory eicosanoids – thromboxane B2 and leukotriene B4 – in BA patients was investigated (Table 3). Regardless of body weight, a statistically significant increase in blood levels of leukotriene B4 and thromboxane B2 was observed in BA patients compared to the control group. In addition, comparison of indicators between groups of BA patients showed a 43 % ($p = 0.001$) increase in leukotriene B4 and a 15 % ($p = 0.001$) increase

TABLE 2

THE COMPOSITION OF FATTY ACIDS AND PLASMALOGENS IN BLOOD PLASMA OF THE EXAMINED PATIENTS

Indicators	Control group ($n = 30$)	Group 1: BA + IBW ($n = 39$)	Group 2: BA + AO ($n = 46$)	Statistical significance level (p)
14:0	0.48 (0.45; 0.57)	0.64 (0.5; 0.93)	1.04 (0.97; 1.23)	$p_{c-2} < 0.001$ $p_{1-2} = 0.035$ $p_{c-1} = 0.044$
15:0	0.17 (0.15; 0.2)	0.18 (0.16; 0.2)	0.18 (0.17; 0.22)	–
16:0	20.3 (19.38; 21.52)	20.16 (19.41; 21.84)	21.21 (19.77; 22.49)	–
17:0	0.23 (0.2; 0.24)	0.25 (0.22 ; 0.26)	0.22 (0.21; 0.24)	–
16:1ω-9	0.39 (0.37; 0.42)	0.35 (0.34; 0.35)	0.47 (0.44; 0.51)	$p_{c-2} < 0.001$ $p_{1-2} = 0.005$
16:1ω-7	1.52 (1.21; 1.75)	1.58 (1.49; 2.36)	1.95 (1.7; 2.43)	$p_{c-2} < 0.001$ $p_{1-2} = 0.004$
17:1	0.15 (0.12; 0.23)	0.17 (0.15; 0.21)	0.21 (0.16; 0.27)	$p_{1-2}<0.001$ $p_{c-2}<0.001$
18:0	6.39 (5.93; 6.8)	6.59 (6.38; 7.13)	7.03 (6.63; 7.45)	–
18:1ω-9	16.89 (15.02; 17.79)	15.76 (15.01; 16.42)	16.57 (15.79; 17.1)	–
18:1ω-7	1.53 (1.36; 1.61)	1.56 (1.39; 1.67)	1.58 (1.48; 1.62)	–
18:2ω-6	36.44 (35.23; 37.64)	38.09 (37.5; 38.95)	35.58 (34.57; 38.21)	–
18:3ω-6	0.3 (0.23; 0.38)	0.28 (0.17; 0.31)	0.4 (0.32; 0.43)	$p_{c-2} = 0.015$ $p_{1-2} = 0.015$
18:3ω-3	0.37 (0.32; 0.41)	0.36 (0.32; 0.47)	0.49 (0.4; 0.54)	$p_{c-2} < 0.001$ $p_{1-2} = 0.038$
20:1ω-7	0.13 (0.11 ; 0.14)	0.22 (0.19; 0.24)	0.21 (0.15; 0.21)	–
20:1ω-9	0.18 (0.15; 0.21)	0.14 (0.12; 0.18)	0.19 (0.15; 0.21)	–
20:2ω-6	0.23 (0.2; 0.29)	0.22 (0.1; 0.2)	0.22 (0.19; 0.25)	–
20:3ω-6	1.12 (0.98; 1.37)	0.81 (0.74; 1.12)	1.19 (1.12; 1.29)	$p_{c-1} = 0.036$ $p_{1-2} = 0.015$
20:4ω-6	5.93 (5.08; 6.54)	5.44 (4.84; 6.81)	5.35 (4.94; 5.96)	–
20:5ω-3	0.88 (0.63; 1.07)	0.83 (0.36; 2.65)	0.54 (0.4; 0.71)	$p_{1-2} = 0.017$ $p_{c-2} = 0.012$
20:4ω-6/20:5ω-3	6.88 (5.35; 9.2)	6.05 (2.57; 9.42)	7.88 (3.91; 13.36)	$p_{1-2} = 0.037$ $p_{c-2} = 0.042$
22:4ω-6	0.17 (0.15; 0.2)	0.18 (0.15; 0.22)	0.12 (0.1; 0.14)	$p_{c-2} < 0.001$ $p_{1-2} < 0.001$

TABLE 2 (*continued*)

Indicators	Control group (*n* = 30)	Group 1: BA + IBW (*n* = 39)	Group 2: BA + AO (*n* = 46)	Statistical significance level (*p*)
22:5ω-3	0.49 (0.4; 0.54)	0.48 (0.3; 0.6)	0.41 (0.29; 0.51)	–
22:6ω-3	2.3 (1.96; 2.54)	2.35 (1.77; 3.06)	1.52 (1.32; 1.65)	$p_{c-2} = 0.012$ $p_{1-2} = 0.035$
16:0DMA	0.39 (0.36; 0.5)	0.46 (0.41; 0.49)	0.27 (0.24; 0.32)	$p_{c-2} = 0.002$ $p_{1-2} < 0.001$
18:0DMA	0.28 (0.23; 0.32)	0.29 (0.22; 0.3)	0.19 (0.17; 0.23)	$p_{1-2} = 0.036$ $p_{c-2} = 0.028$
18:1DMA	0.14 (0.13; 0.15)	0.12 (0.1; 0.16)	0.11 (0.1; 0.12)	–
20:0DMA	0.18 (0.15; 0.18)	0.13 (0.08; 0.19)	0.18 (0.17; 0.2)	–
DMA16:0/FAME16:0	1.91 (1.64; 2.37)	2.21 (1.93; 2.4)	1.32 (1.09; 1.54)	$p_{c-2} = 0.002$ $p_{1-2} < 0.001$
DMA18:0/FAME18:0	4.03 (3.44; 4.82)	3.68 (3.15; 5.06)	2.76 (2.45; 3.38)	$p_{c-2} < 0.001$ $p_{1-2} = 0.013$

Note. Descriptive statistics are presented as Me (L_q; U_q), where Me is median, L_q is lower quartile, U_q is upper quartile; p_{c-1} is statistical significance of differences between control group and Group 1; p_{c-2} is statistical significance of differences between control group and group 2; p_{1-2} is statistical significance of differences between Groups 1 and 2. Values are given for $p < 0.05$ only.

TABLE 3
THE LEVEL OF EICOSANOIDS IN BLOOD PLASMA OF THE EXAMINED PATIENTS

Indicators	Control group (*n* = 30)	Group 1: BA + IBW (*n* = 39)	Group 2: BA + AO (*n* = 46)	Statistical significance level (*p*)
Lukotriene B4, pg/ml	11.28 (10.43; 12.43)	17.87 (16.4; 18.65)	25.61 (23.03; 29.9)	$p_{c-1} < 0.001$ $p_{c-2} < 0.001$ $p_{1-2} = 0.001$;
Thromboxane B_2, pg/ml	62.15 (56.3; 70.85)	79.9 (78.12; 90.32)	90.24 (87.47; 98.54)	$p_{c-1} = 0.003$ $p_{c-2} < 0.001$ $p_{1-2} = 0.001$

Note. Descriptive statistics are presented as Me (L_q; U_q), where Me is median, L_q is lower quartile, U_q is upper quartile; p_{c-1} is statistical significance of differences between control group and Group 1; p_{c-2} is statistical significance of differences between control group and Group 2; p_{1-2} is statistical significance of differences between Groups 1 and 2. Values are given for $p < 0.05$ only.

in thromboxane B2 if obesity was present. The findings suggest a pronounced inflammatory response in BA associated with obesity.

The presence of the disbalance in the FA composition, formation disorder of their oxidized metabolites and plasmalogen synthesis disorder can provoke the development of chronic inflammation, oxidative stress, which can lead to increased respiratory dysfunction.

In order to establish the role of individual lipids in the development of small airway dysfunction in mild BA with NBW and associated with alimentary-constitutional obesity, a correlation analysis was performed (Tables 4, 5). Correlations were evaluated with regard to PFT parameters reflecting the functional state of small airways.

According to body plethysmography, the criteria for small airway dysfunction are considered to be an increase in RV more than 140 % and RV/TLC more than 125 % of the target values as signs of "air traps", and an increase in FRC more than 130 % of the target value – as an indicator of hyperinflation [19]. Indirect signs of small airway dysfunction in BA also include changes in spirometry. Decreased FVC level is suggested by some authors to be considered as an indicator of «air traps» presence, and $MMEF_{25-75}$ is suggested to be used as a marker of early small airway dysfunction [20].

In the 1st group of patients with BA and NBW, associations were established between the levels of SFA and FWD indicators reflecting the state of small airways (Table 4).

TABLE 4

CORRELATIONS BETWEEN INDICATORS OF DYSFUNCTION OF SMALL AIRWAYS AND FATTY ACIDS, PLASMALOGENS IN PATIENTS OF GROUP 1(SPEARMAN CORRELATION, *r*)

Indicators	FVC%	FEV_1%	$MMEF_{25-75}$%	FRC_{plet}%	RV%	TLC%	RV/TLC%
14:0	–	–	–	0.76 $p = 0.011$	0.59 $p = 0.023$	–	–
15:0	–	–	–	–	0.56 $p = 0.035$	–	0.58 $p = 0.027$
16:0	–	–	–	–	0.57 $p = 0.047$	–	0.6 $p = 0.021$
18:0	–	–	–	0.53 $p = 0.046$	–	–	–
17:1	–	–	–	–	–	0.64 $p = 0.013$	–
16:1ω-9	–	–	–	–	0.57 $p = 0.019$	0.53 $p = 0.046$	–
18:1ω-9	–	–	–	–0.55 $p = 0.036$	–	–	–
18:1ω-7	–	–	–	0.83 $p = 0.011$	–	–	–
18:3ω-3	0.73 $p = 0.003$	0.81 $p < 0.001$	–	–	–	–	–
18:3ω-6	0.57 $p = 0.031$	–	–	–	–	–	–
20:1ω-9	–	–0.69 $p = 0.006$	–0.71 $p = 0.011$	–	–	–	–
20:2ω-6	–	–	–	–0.65 $p = 0.011$	–	–	–
20:3ω-6	0.59 $p = 0.025$	–	–		–	–	–
20:4ω-6		–	–	–0.6 $p = 0.013$	–	–	–
22:4ω-6	–0.81 $p = 0.042$	–	–	–0.59 $p = 0.025$	–	–	–
22:5ω-3	–	–	–	–	–0.62 $p = 0.022$	–	–0.58 $p = 0.028$
22:6ω-3	–	–	–	–	–0.65 $p = 0.011$	–	–0.66 $p = 0.009$
16:0 DMA	–0.55 $p = 0.038$	–0.79 $p = 0.001$	–	–	0.57 $p = 0.029$	–	–
DMA16:0/FAME16:0		–0.88 $p < 0.001$	–	–	–	–	–
18:0 DMA	–0.66 $p = 0.009$	–0.61 $p = 0.019$	–	–	–	–	–

TABLE 4 (*continued*)

Indicators	FVC%	FEV_1%	$MMEF_{25-75}$%	FRC_{plet}%	RV%	TLC%	RV/TLC%
18:1 DMA	–0.53 $p = 0.038$	–	–	–	–	–	–
DMA18:0/FAME18:0	–0.59 $p = 0.023$	–0.59 $p = 0.023$	–	–	–	–	–
20:0 DMA	0.57 $p = 0.029$	–	–	–	–	–	–

Note. Only statistically significant correlations between indicators at $p < 0.05$ are shown.

TABLE 5

CORRELATIONS BETWEEN INDICATORS OF DYSFUNCTION OF SMALL AIRWAYS AND FATTY ACIDS, PLASMALOGENS IN PATIENTS OF GROUP 2 (SPEARMAN CORRELATION, *r*)

Indicators	FVC%	FEV_1%	$MMEF_{25-75}$%	FRC_{plet}%	RV%	TLC%	RV/TLC%
14:0	–	–	–	–	–	–	–
15:0	0.49 $p = 0.019$	0.48 $p = 0.022$	–	–	–	–	–
16:0	–0.66 $p < 0.001$	–	–	–	–	–	–
17:1	–	–	–	–0.59 $p = 0.019$	–	–0.54 $p = 0.036$	–
18:0	–0.47 $p = 0.024$	–	–	0.32 $p = 0.041$	–	–	–
20:1ω-7	–0.51 $p = 0.005$	–0.43 $p = 0.022$	–0.45 $p = 0.005$	–	–	–0.70 $p < 0.001$	0.52 $p = 0.009$
20:4ω-6	–	–	–	–	–	–	0.73 $p = 0.017$
20:5ω-3	–	–	–	–	0,39 $p = 0.034$	0.47 $p = 0.009$	–
20:4ω-6/20:5ω-3	–	–	–	–	–	–	0.78 $p = 0.016$
22:4ω-6	–	–	0.29 $p = 0.044$	–	0.29 $p = 0.046$	–	–
22:5ω-3	–	–	–	–	–	–	–0.58 $p = 0.028$
22:6ω-3 a	–	–	–	–	–	–	–0.66 $p = 0.009$
DMA18:0/FAME18:0	–	–	–	–	–	–	–0.41 $p = 0.029$
20:0 DMA	–	–	–	–0.47 $p = 0.024$	–0.42 $p = 0.048$	–	–
Thromboxane B_2, pg/ml	–0.89 $p < 0.001$	–	–	–0.65 $p = 0.011$	–	–0.86 $p < 0.001$	–

Note. Only statistically significant correlations between indicators at $p < 0.05$ are shown.

Positive correlations of myristic (14:0) and stearic (18:0) acids with FRC_{plet}; myristic, pentadecylic (15:0), and palmitic (16:0) acids with RV; and pentadecylic and palmitic acids with RV/TLC were found.

Positive correlations of MFAs were determined, specifically heptadecenoic (17:1) with TLC; hexadecenoic (16:1ω-9) with RV and TLC; and octadecaenoic (18:1ω-7) with FRC_{plet}. Negative correlations were determined between oleic acid (18:1ω-9) and FRC, eicosenoic acid (20:1ω-9) and FEV_1, $MMEF_{25-75}$.

Assotiations with PFT indicators were also revealed for PUFAs. For ω-3 PUFAs, positive correlations were observed between α-linolenic acid (18:3ω-3), FVC and FEV_1 and negative correlations between docosapentaenoic (22:5ω-3) and docosahexaenoic (22:6ω-3) acids and RV, RV/TLC. Among ω-6 PUFAs, positive correlations of γ-linolenic (18:3ω-6) and digomo-γ-linolenic (20:3ω-6) PUFAs with FVC were observed; negative correlations of eicosadiene (20:2ω-6) and arachidonic (20:4ω-6) PUFAs with FRC_{plet}, and adrenoic (22:4ω-6) PUFA with FVC and FRC_{plet}.

Plasmalogens levels were also correlated with the examined PFT indicators. So, DMA16:0, DMA18:0, and DMA18:0/FAME18:0 had negative correlations with FVC and FEV_1; DMA18:1 with FVC; and DMA16:0/FAME16:0 with FEV_1. Direct correlations were established between DMA16:0 and RV, DMA20:0 and FVC.

In Group 2 (Table 5), assotiation between SFA and external respiratory function were determined. In particular, pentadecylic acid (15:0) had a positive correlation with FVC and FEV_1, while palmitic (16:0) and stearic (18:0) acids had a negative correlation with FVC and a positive correlation with FRC_{plet}. Of the MFAs, heptadecenoic acid (17:1) had negative correlations with FRC_{plet} and TLC, and eicosenoic acid (20:1ω-7) had negative correlations with FVC, FEV1, $MMEF_{25–75}$, and TLC. A positive correlation was observed between 20:1ω-7 and RV/TLC. Of the ω-3 family PUFAs, docosapentaenoic (22:5ω-3) and docosahexaenoic (22:6ω-3) acids had negative correlations with RV/TLC.

Positive correlations were established between arachidonic acid (20:4ω-6) and RV/TLC, adrenoic acid (22:4ω-6) and $MMEF_{25–75}$, and RV. Negative correlations were found between DMA20:0 and FRC_{plet}, RV levels; DMA18:0/FAME18:0 and RV/TLC. We should note the negative correlations of thromboxane B_2 level with such an indicator of PFT as FVC, and indicators reflecting the state of small airways, – FRC_{plet} and TLC.

The established features of the composition of fatty acids, eicosanoids, plasmalogens, their link with PFT indicators demonstrate their participation in the progression of bronchobstruction, formation of air traps and hyperinflation in BA.

RESULTS DISCUSSION

The changes in PFT indicators according to spirometry and body plethysmography revealed in the study show the presence of generalized bronchial obstruction in patients with different body weight and with mild partially controlled asthma. Furthermore, in patients with obesity-associated bronchial asthma, a decrease in the levels of FEV_1, $MMEF_{25–75}$ and an increase in RV were observed, which indicate the development of small airway dysfunction in patients of this group.

When studying the lipid composition of blood plasma by the level of fatty acids, eicosanoids and plasmalogens, the peculiarities of the lipidome in groups of patients with BA were identified. Moreover, the dynamics of blood plasma lipid changes indicates the presence of a systemic chronic inflammatory process in patients with asthma, aggravated by obesity. It has been previously shown that inflammation in BA associated with AO is mediated by hyperproduction of leptin, pro-inflammatory cytokines that lead to systemic chronic low intensity inflammation [21].

In patients with bronchial asthma, only an increase in the proportion of saturated myristic acid was noted. At the same time, correlations with PFT indicators have been established for the majority of SFAs, indicating their involvement in the development of bronchial obstruction and small airway dysfunction. Saturated fatty acids (myristic, stearic, palmitic), on the one hand, play a structural role affecting the packing density of the cell membrane; on the other hand, an increase in their level in biological substrates is always an unfavorable sign from the position of cell signaling functions, since in this case the membrane becomes less susceptible to receptor expression and synthesis of immune mediators. In lung surfactant, saturated fatty acids esterified into complex lipids form a more structured packing of phospholipids, which increases the density of surfactant [22]. Therefore, the chemical composition of surfactant, its enrichment of SFAs can influence the properties and structure of small airways.

Increased levels of monoenoic palmitoleic acid and hexadecenoic acid were observed in patients with bronchial asthma and obesity. MFAs are part of the structure of every cell and play an essential role in the regulation of lipid metabolism [23]. Palmitoleic acid is known to function as a lipokine lipid with hormone-like biological activity. Palmitoleic acid can directly participate in the regulation of insulin resistance and metabolic disorders [24]. In a study by D. Mozaffarian et al. it was shown that increased levels of palmitoleic acid are associated with a better metabolic profile and low development of diabetes [24]. The increased level of palmitoleic acid in patients with bronchial asthma and obesity detected in our study probably indicates a compensatory response of the organism aimed at maintaining lipid homeostasis in order to minimize metabolic disorders.

In the 1st group of patients against the background of normal level of MFA, as well as in the 2nd group MFA associative relations of ω-9 and ω-7 families with PFT indicators characterizing the state of small airways were established, which allows to conclude about the MFA influence of ω-9 and ω-7 families on the formation of small airway dysfunction.

Differences in PUFA composition in groups of BA patients with NBW (Group 1) and BA associated with obesity (Group 2) were identified. In group 2, a change in the PUFA levels of the ω-3 and ω-6 families was observed. Against

the background of decreased levels of eicosapentaenoic (20:5ω-3), docosahexaenoic (22:6ω-3) acids, there was an increase in γ-linolenic (18:3ω-6) acid, digomo-γ-linolenic (20:3ω-6) LC compared to control and Group 1.

Polyunsaturated fatty acids are responsible for increasing the fluidity and viscosity of the cell membrane. PUFAs of the ω-6 family are the main substrates for the synthesis of pro-inflammatory, bronchoconstrictor, vasoconstrictor mediators and precursors of endocannabinoids, lipoxins, while PUFAs of the ω-3 family are considered as precursors of anti-inflammatory, pro-resolving, vasodilatory mediators. ω-3 PUFAs are known to influence inflammatory markers, reducing their levels (C-reactive protein, IL-6, tumor necrosis factor α). Eicosapentaenoic acid (20:5ω-3) is a substrate for oxylipins synthesis (maresins, resolvins, protectins), which are anti-inflammatory, pro-resolving and anti-proliferative mediators providing the most important competing cascade in inflammation towards its resolution [25]. Balance shift between arachidonic (20:4ω-6) and eicosopentaenoic (20:5ω-3) FAs shows disorders in the eicosanoid cycle and, consequently, a high risk of inflammation, which is a prognostically unfavorable sign of increased pro-inflammatory reactions that may lead to the development of small airway dysfunction in the combined course of BA [26].

Interesting correlations were established between the PFT indicators reflecting the state of airways and the composition of PUFAs of the ω-3 and ω-6 families in the groups. For example, for patients with BA and NBW, the greatest number of relations with FVC and FEV_1 were noted. These indicators are known to reflect the presence or absence of bronchial obstruction at different levels and can act as indicators of airway remodeling [27].

In Group 2, in patients with BA and obesity, the highest number of direct relations with PUFAs of the ω-6 family and negative relations with PUFAs of the ω-3 family were determined for indicators reflecting the state of small airways (FRC_{plet}, RV, TLC, RV/TLC). In contrast to Group 1, in the combined course of BA, correlations of eicosopentaenoic acid levels, 20:4ω-6/20:5ω-3 ratio with RV, RV/TLC indicators were established.

The results demonstrate the involvement of PUFAs in the development and progression of small airway inflammation and in the formation of air traps and hyperinflation.

Notably, thromboxane B_2 and leukotriene B_4 were increased in the blood of BA patients regardless of body weight compared to the control group. Eicosanoids as derivatives of arachidonic acid contribute to the development of a marked inflammatory response [26]. In patients with BA and AO, the level of leukotriene B_4 was higher relative to the patients of Group 1. The established inverse correlation between thromboxane B_2 levels and FVC, FRC_{plet}, and TLC in obesity-associated BA indicates the involvement of thromboxane in the development of small airway dysfunction in this group of patients.

The level of plasmalogens in Group 1 did not differ from that of controls. Despite this, negative correlations were found between plasmalogens 16:0DMA, 18:0DMA, 18:1DMA, and 20:0DMA with PFT indicators (FVC, FEV_1). Meanwhile, in Group 2 (bronchial asthma with obesity), the decrease in the levels of plasmalogens containing 16:0 and 18:0 aldehydes and 18:0DMA/18:0FAME ratio was combined with the presence of negative correlations between the indicators reflecting the state of small airways (FRC_{plet}, RV, RV/TLC) and the levels of 20:0DMA and 18:0DMA/18:0FAME. The established correlations indicate the involvement of plasmalogens in the development and progression of small airway inflammation and in the formation of air traps and hyperinflation. Plasmalogens are known to increase the viscosity and tension of lung surfactant. Since the lungs are a direct target of reactive oxygen species, plasmalogens, which are part of surfactant, protect the lungs from their aggressive effects and other environmental factors [28–30]. In the studies of J.E. Sordillo et al. plasmalogens are identified as possible mediators of changes in lung function in people with asthma, including age-related, and can also serve as a potential pharmacological target to improve PFT in people with asthma [13].

Thus, the presence of a large number of positive and negative correlations between lipid mediators and PFT parameters in patients with BA and NBW can be regarded as a more active systemic response to the development of the disease, aimed at preserving internal homeostasis. The association of BA with obesity causes a decrease in the body defenses and disease progression, which is reflected in clinical, laboratory and functional parameters. The assotiations between the indicators of small airway dysfunction and blood plasma lipidome indicate the importance of fatty acids, plasmalogens and eicosanoids in the regulation of the functional state of small airway in BA.

CONCLUSION

Small airway dysfunction develops in patients with mild bronchial asthma associated with abdominal obesity against the background of generalized bronchial obstruction. An important pathogenetic link in the formation of small airway dysfunction is impaired fatty acid metabolism and plasmalogens synthesis, increased formation of inflammatory lipid mediators such as thromboxane and leukotriene. The combined course of BA and alimentary-constitutional obesity is characterized by increased levels of SFAs, MFAs, PUFAs of the ω-6 family and decreased levels of PUFAs of the ω-3 family in plasma. Disorder in the synthesis of lipid mediators (plasmalogens and eicosanoids) in obesity-associated BA determines changes in the molecular mechanisms of immune signaling and antioxidant processes, which underlies the development of chronic systemic and local inflammation in obesity-associated BA. The presence of high correlation of blood lipidome components with functional indices of respiratory organs indicates the pathogenetic role of fatty acids and inflammatory lipid mediators in the formation and progression of small airway dysfunction in BA in combination with obesity, and, consequently, in the aggravation of BA course. Eicosopentaenoic acid, the ratio of PUFAs of ω-6 and ω-3 families (20:4ω-6/20:5ω-3) and thromboxane B_2, which have correlations with markers of small airway

dysfunction characteristic for BA in combination with obesity, may be biomarkers of the formation and progression of airway dysfunction and, consequently, of the aggravation of the course of bronchial asthma. Further studies of lipid triggers of small airway dysfunction will allow the development of technologies to predict the course and control of bronchial asthma.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

Source of funding

The study was carried out within the research work framework "Pathogenetic mechanisms of respiratory system diseases formation", state registration number AAAA-A19-119100290026-5.

REFERENCES

1. Soloveva IA, Sobko EA, Demko IV, Kraposhina AY, Gordeeva NV, Loktionova MM. Asthma and obesity. *Terapevticheskii arkhiv.* 2017; 89(3): 116-120. (In Russ.). doi: 10.17116/terarkh2017893116-120

2. Gusova ZR, Dzantieva EO, Khripun IA. Immunological aspects of obesity. *Almanac of Clinical Medicine.* 2015; 1: 30-35. (In Russ.).

3. Gnoevykh VV, Shorokhova YuA, Smirnova AYu, Peskov AB, Razin VA. Peculiarities of bronchial asthma clinical course in smokers with small airway diseases. *Ulyanovsk Medico-Biological Journal.* 2020; 1: 8-21. (In Russ.). doi: 10.34014/2227-1848-2020-1-8-21

4. Postma DS, Brightling C, Baldi S, van den Berge M, Fabbri LM, Gagnatelli A, et al. ATLANTIS study group. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): Baseline data from a prospective cohort study. *Lancet Respir Med.* 2019; 7(5): 402-416. doi: 10.1016/S2213-2600(19)30049-9

5. Fassakhov RS. Significant role of small respiratory tracts: new possibilities of cyclesonide in therapy of bronchial asthma. *Medical Council.* 2017; (18): 56-60. (In Russ.). doi: 10.21518/2079-701X-2017-18-56-60

6. Mineeva EE, Antonyuk MV, Yurenko AV, Gvozdenko TA, Uksumenko AA. Small airways dysfunction and the state of lung function in mild asthma. *Bulletin Physiology and Pathology of Respiration.* 2020; (78): 76-83. (In Russ.). doi: 10.36604/1998-5029-2020-78-76-83

7. Kraposhina AY, Sobko EA, Demko IV, Kacer AB, Kazmerchuk OV, Abramov YI. Modern understanding of bronchial asthma with fixed airflow obstruction. *Terapevticheskii arkhiv.* 2021; 93(3): 337-342. (In Russ.). doi: 10.26442/00403660.2021.03.200661

8. Grainge CL, Davies DE. Epithelial injury and repair in airways diseases. *Chest.* 2013; 144(6): 1906-1912. doi: 10.1378/chest.12-1944

9. Pietiläinen KH, Róg T, Seppänen-Laakso T, Virtue S, Gopalacharyulu P, Tang J, et al. Association of lipidome remodeling in the adipocyte membrane with acquired obesity in humans. *PLoS Biol.* 2011; 9(6): e1000623. doi: 0.1371/journal.pbio.1000623

10. Wynalda KM, Murphy RC. Low-concentration ozone reacts with plasmalogen glycerophosphoethanolamine lipids in lung surfactant. *Chem Res Toxicol.* 2010; 23(1): 108-117. doi: 10.1021/tx900306p

11. Karateev AE, Aleinikova TL. Eicosanoids and inflammation. *Modern Rheumatology Journal.* 2016; 10(4): 73-86. (In Russ.). doi: 10.14412/1996-7012-2016-4-73-86

12. Bozelli JC Jr, Azher S, Epand RM. Plasmalogens and chronic inflammatory diseases. *Front Physiol.* 2021; 12: 730829. doi: 10.3389/fphys.2021.730829

13. Sordillo JE, Lutz SM, Kelly RS, McGeachie MJ, Dahlin A, Tantisira K, et al. Plasmalogens mediate the effect of age on bronchodilator response in individuals with asthma. *Front Med.* 2020; 7: 38. doi: 10.3389/fmed.2020.00038

14. Hajeyah AA, Griffiths WJ, Wang Y, Finch AJ, O'Donnell VB. The biosynthesis of enzymatically oxidized lipids. *Front Endocrinol (Lausanne).* 2020; 11: 591819. doi: 10.3389/fendo.2020.591819

15. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: A review. *J Adv Res.* 2018; 11: 23-32. doi: 10.1016/j.jare.2018.03.005

16. Dean JM, Lodhi IJ. Structural and functional roles of ether lipids. *Protein Cell.* 2018; 9(2): 196-206. doi: 10.1007/s13238-017-0423-5

17. Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006; 100(4): 616-621. doi: 10.1016/j.rmed.2005.08.012

18. Medical statistics. *Dictionary of statistical terms.* URL: https://medstatistic.ru/theory/odds_ratio.html [date of acsess: 01.06.2022]. (In Russ.).

19. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005; 26: 948-968. doi: 10.1183/09031936.05.00035205

20. Aisanov ZR, Kalmanova EN. The lesion of small airways i patients with asthma: New data, new paradigm. *Prakticheskaya pulmonologiya.* 2019; 1: 6-14. (In Russ.).

21. Yurenko AV, Antonyuk MV, Mineeva EE, Novgorodtseva TP, Khodosova KK. Features of cytokine and adipokine regulation in asthma associated with obesity. *Russian Open Medical Journal.* 2019; 8(2): e0203. doi: 10.15275/rusomj.2019.0203

22. Denisenko YK, Novgorodtseva TP, Zhukova NV, Antonuk MV, Lobanova EG, Kalinina EP. Association of fatty acid metabolism with systemic inflammatory response in chronic respiratory diseases. *Biomeditsinskaya khimiya.* 2016; 62(3): 341-347. (In Russ.). doi: 10.18097/PBMC20166203341

23. Volovik VT, Leonidova TV, Korovina LM, Blokhina NA, Kasarina NP. Comparison of the fatty acid composition of various edible oils. *Mezhdunarodnyy zhurnal prikladnykh i fundamental'nykh issledovaniy.* 2019; 5: 147-152. (In Russ.). doi: 10.17513/mjpfi.12754

24. Mozaffarian D, Cao H, King IB, Lemaitre RN, Song X, Siscovick DS, et al. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: A cohort study. *Ann Intern Med.* 2010; 153(12): 790-799. doi: 10.7326/0003-4819-153-12-201012210-00005

25. Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. *Prostaglandins Other Lipid Mediat.* 2012; 99(3-4): 57-67. doi: 10.1016/j.prostaglandins.2012.09.006

26. Denisenko YK, Lobanova EG, Novgorodtseva TP, Gvozdenko TA, Nazarenko AV. The role of arachidonic acid metabolites

(endocannabinoids and eicosanoids) in the immune processes: A review. *Int J Chem Biomed Sci*. 2015; 1(3): 70-78.

27. Yuan H, Liu X, Li L, Wang G, Liu C, Zeng Y, et al. Clinical and pulmonary function changes in cough variant asthma with small airway disease. *Allergy Asthma Clin Immunol*. 2019; 15: 41. doi: 10.1186/s13223-019-0354-1

28. Zhuo R, Rong P, Wang J, Parvin R, Deng Y. The potential role of bioactive plasmalogens in lung surfactant. *Front Cell Dev Biol*. 2021; 9: 618102. doi: 10.3389/fcell.2021.618102

29. Zoeller RA, Grazia TJ, LaCamera P, Park J, Gaposchkin DP, Farber HW. Increasing plasmalogen levels protects human endothelial cells during hypoxia. *Am J Physiol Heart Circ. Physiol.* 2002; 283: H671-H679. doi: 10.1152/ajpheart.00524.2001

30. Novgorodtseva TP, Kytikova OY, Gvozdenko TA, Antonyuk MV. Prospects for the use of natural alkyl-glycerols in targeted therapy of bronchial asthma associated with obesity (review). *Siberian Scientific Medical Journal.* 2018; 38(6): 103-110. (In Russ.). doi: 10.15372/SSMJ20180615

ЛИТЕРАТУРА

1. Соловьева И.А., Собко Е.А., Демко И.В., Крапошина А.Ю., Гордеева Н.В., Локтионова М.М. Бронхиальная астма и ожирение. *Терапевтический архив*. 2017; 89(3): 116-120. doi: 10.17116/terarkh2017893116-120

2. Гусова З.Р., Дзантиева Е.О., Хрипун И.А. Иммунологические аспекты ожирения. *Альманах клинической медицины*. 2015; 1: 30-35.

3. Гноевых В.В., Шорохова Ю.А., Смирнова А.Ю., Песков А.Б., Разин В.А. Особенности клинического течения бронхиальной астмы у курильщиков с поражением малых дыхательных путей. *Ульяновский медико-биологический журнал*. 2020; 1: 8-21. doi: 10.34014/2227-1848-2020-1-8-21

4. Postma DS, Brightling C, Baldi S, van den Berge M, Fabbri LM, Gagnatelli A, et al. ATLANTIS study group. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): Baseline data from a prospective cohort study. *Lancet Respir Med*. 2019; 7(5): 402-416. doi: 10.1016/S2213-2600(19)30049-9

5. Фассахов Р.С. Большая роль малых дыхательных путей: новые возможности циклесонида в терапии бронхиальной астмы. *Медицинский совет*. 2017; (18): 56-60. doi: 10.21518/2079-701X-2017-18-56-60

6. Минеева Е.Е., Антонюк М.В., Юренко А.В., Гвозденко Т.А., Уксуменко А.А. Дисфункция малых дыхательных путей и состояние легочной функции при легкой бронхиальной астме. *Бюллетень физиологии и патологии дыхания*. 2020; (78): 76-83. doi: 10.36604/1998-5029-2020-78-76-83

7. Крапошина А.Ю., Собко Е.А., Демко И.В., Кацер А.Б., Казмерчук О.В., Абрамов Ю.И. Современное представление о бронхиальной астме с фиксированной обструкцией. *Терапевтический архив*. 2021; 93(3): 337-342. doi: 10.26442/00403660.2021.03.200661

8. Grainge CL, Davies DE. Epithelial injury and repair in airways diseases. *Chest*. 2013; 144(6): 1906-1912. doi: 10.1378/chest.12-1944

9. Pietiläinen KH, Róg T, Seppänen-Laakso T, Virtue S, Gopalacharyulu P, Tang J, et al. Association of lipidome remodeling in the adipocyte membrane with acquired obesity in humans. *PLoS Biol*. 2011; 9(6): e1000623. doi: 0.1371/journal.pbio.1000623

10. Wynalda KM, Murphy RC. Low-concentration ozone reacts with plasmalogen glycerophosphoethanolamine lipids in lung surfactant. *Chem Res Toxicol*. 2010; 23(1): 108-117. doi: 10.1021/tx900306p

11. Каратеев А.Е., Алейникова Т.Л. Эйкозаноиды и воспаление. *Современная ревматология*. 2016; 10(4): 73-86. doi: 10.14412/1996-7012-2016-4-73-86

12. Bozelli JC Jr, Azher S, Epand RM. Plasmalogens and chronic inflammatory diseases. *Front Physiol*. 2021; 12: 730829. doi: 10.3389/fphys.2021.730829

13. Sordillo JE, Lutz SM, Kelly RS, McGeachie MJ, Dahlin A, Tantisira K, et al. Plasmalogens mediate the effect of age on bronchodilator response in individuals with asthma. *Front Med.* 2020; 7: 38. doi: 10.3389/fmed.2020.00038

14. Hajeyah AA, Griffiths WJ, Wang Y, Finch AJ, O'Donnell VB. The biosynthesis of enzymatically oxidized lipids. *Front Endocrinol (Lausanne)*. 2020; 11: 591819. doi: 10.3389/fendo.2020.591819

15. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: A review. *J Adv Res.* 2018; 11: 23-32. doi: 10.1016/j.jare.2018.03.005

16. Dean JM, Lodhi IJ. Structural and functional roles of ether lipids. *Protein Cell.* 2018; 9(2): 196-206. doi: 10.1007/s13238-017-0423-5

17. Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006; 100(4): 616-621. doi: 10.1016/j.rmed.2005.08.012

18. Медицинская статистика. *Словарь статистических терминов*. URL: https://medstatistic.ru/theory/odds_ratio.html [дата доступа: 01.06.2022].

19. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005; 26: 948-968. doi: 10.1183/09031936.05.00035205

20. Айсанов З.Р., Калманова Е.Н. Поражение малых дыхательных путей при бронхиальной астме: новые данные, новая парадигма. *Практическая пульмонология*. 2019; 1: 6-14.

21. Yurenko AV, Antonyuk MV, Mineeva EE, Novgorodtseva TP, Khodosova KK. Features of cytokine and adipokine regulation in asthma associated with obesity. *Russian Open Medical Journal.* 2019; 8(2): e0203. doi: 10.15275/rusomj.2019.0203

22. Денисенко Ю.К., Новгородцева Т.П., Жукова Н.В., Антонюк М.В., Лобанова Е.Г., Калинина Е.П. Ассоциация метаболизма жирных кислот с системной воспалительной реакцией при хронических заболеваниях органов дыхания. *Биомедицинская химия*. 2016; 62(3): 341-347. doi: 10.18097/PBMC20166203341

23. Воловик В.Т., Леонидова Т.В., Коровина Л.М., Блохина Н.А., Касарина Н.П. Сравнение жирнокислотного состава различных пищевых масел. *Международный журнал прикладных и фундаментальных исследований*. 2019; 5: 147-152. doi: 10.17513/mjpfi.12754

24. Mozaffarian D, Cao H, King IB, Lemaitre RN, Song X, Siscovick DS, et al. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: A cohort study. *Ann Intern*

Med. 2010; 153(12): 790-799. doi: 10.7326/0003-4819-153-12-201012210-00005

25. Giudetti AM, Cagnazzo R. Beneficial effects of n-3 PUFA on chronic airway inflammatory diseases. *Prostaglandins Other Lipid Mediat*. 2012; 99(3-4): 57-67. doi: 10.1016/j.prostaglandins.2012.09.006

26. Denisenko YK, Lobanova EG, Novgorodtseva TP, Gvozdenko TA, Nazarenko AV. The role of arachidonic acid metabolites (endocannabinoids and eicosanoids) in the immune processes: A review. *Int J Chem Biomed Sci*. 2015; 1(3): 70-78.

27. Yuan H, Liu X, Li L, Wang G, Liu C, Zeng Y, et al. Clinical and pulmonary function changes in cough variant asthma with small airway disease. *Allergy Asthma Clin Immunol*. 2019; 15: 41. doi: 10.1186/s13223-019-0354-1

28. Zhuo R, Rong P, Wang J, Parvin R, Deng Y. The potential role of bioactive plasmalogens in lung surfactant. *Front Cell Dev Biol*. 2021; 9: 618102. doi: 10.3389/fcell.2021.618102

29. Zoeller RA, Grazia TJ, LaCamera P, Park J, Gaposchkin DP, Farber HW. Increasing plasmalogen levels protects human endothelial cells during hypoxia. *Am J Physiol Heart Circ. Physiol.* 2002; 283: H671-H679. doi: 10.1152/ajpheart.00524.2001

30. Новгородцева Т.П., Кытикова О.Ю., Гвозденко Т.А., Антонюк М.В. Перспективы использования природных алкилглицеринов в таргетной терапии бронхиальной астмы, ассоциированной с ожирением (обзор литературы). *Сибирский научный медицинский журнал*. 2018; 38(6): 103-110. doi: 10.15372/SSMJ20180615

Information about the authors

Alla V. Yurenko – Cand. Sci. (Med.), Research Officer at the Laboratory of Rehabilitation Treatment, Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, e-mail: yurenko_alla@mail.ru, https://orcid.org/0000-0003-0396-6380

Tatyana P. Novgorodtseva – Dr. Sc. (Biol.), Professor, Chief Research Officer at the Laboratory of Biomedical Research, Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, e-mail: nauka@niivl.ru, https://orcid.org/0000-0002-6058-201x

Yulia K. Denisenko – Dr. Sc. (Biol.), Head of the Laboratory of Biomedical Research, Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, e-mail: karaman@inbox.ru, https://orcid.org/0000-0003-4130-8899

Marina V. Antonyuk – Dr. Sc. (Med.), Professor, Head of the Laboratory of Rehabilitation Treatment, Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, e-mail: antonyukm@mail.ru, https://orcid.org/0000-0002-2492-3198

Elena E. Mineeva – Cand. Sc. (Med.), Research Officer at the Laboratory of Rehabilitation Treatment, Vladivostok Branch of the Far Eastern Scientific Center of Physiology and Pathology of Respiration – Research Institute of Medical Climatology and Rehabilitation Treatment, e-mail: elmineeva@yandex.ru, https://orcid.org/0000-0002-4286-2827