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Intraerythrocyte Non-Protein-Bound Iron in Children with Bronchopulmonary Pathology

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Abstract

A total of 230 children having bronchopulmonary pathology (BPP) were examined. Patients were divided into 4 groups according to their intraerythrocyte non-protein-bound iron (IE-NPBI) levels. We investigated the relationship of the IE-NPBI level with parameters of respiratory function (RF) tests, the severity of comorbidities, and level of other free intracellular ions, such as copper, zinc, and magnesium. The pronounced increase in IE-NPBI level was typical for patients with the connective tissue dysplasia, often accompanied by mitral valve prolapse, osteopenia, and mineral metabolism violation. The severe comorbid diagnoses were typical for patients with reduced levels of IE-NPBI (chronic cor pulmonale, tuberculosis infection). The largest number of comorbidities, aggravating the underlying disease, took place in the group of patients with a significant reduction in IE-NPBI level. A significant increase in IE-NPBI level, as well as a marked reduction of IE-NPBI level, was an unfavorable factor for the underlying disease. We found a correlation between IE-NPBI level and parameters of RF-test in patients with moderate increase in IE-NPBI level.

Keywords: *children; bronchopulmonary pathology; intraerythrocyte non-protein-bound iron; respiratory function.*

Introduction

Iron is an essential component of hundreds of proteins and enzymes. The main functions of iron include oxygen transport and storage, electron transport, energy metabolism and activation of the redox enzymes. Iron is an integral part of cytochromes *P-450, a, b,* and *c* [1]. Despite the variety of cellular forms in different organs, the regeneration processes are universal, and blood-forming organs are no exception. Structural and metabolic disorders of red blood cells (RBCs) are found in various pathologies and may be of hereditary origin or the result of such factors as immune and autoimmune disorders, violations of the erythrocyte membrane permeability, hemorrhage, hypoxia, burns and other factors [2].

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In all tissues, the content of non protein-bound iron (NPBI) is approximately equal, about 5–6 μg per gram of fresh weight, which corresponds to 100 μM/kg tissue. With an excess of iron and increasing free radical process in tissues, ferritin turns into hemosiderin - a slightly soluble complex of iron crystals uncovered with a protein layer; it contains the denatured ferritin protein in relatively low concentration and lipids. Iron mobilizes from it very slowly, and this process is apparently not subject to strict regulation [3]. The mechanism of iron release from ferritin in the presence of the activated neutrophils and xanthine oxidase underlies the pathogenesis of the oxygen-deficient states and inflammatory processes [3-5]. It is known that tissue hypoxia results in an increase of free iron and is closely correlated with the accumulation of lipid peroxidation products (LPP), the stopping of ATP synthesis, an activation of phospholipase, an increase in intracellular membrane permeability, and releasing Fe^{2+}ions from the membrane compartments with entrance into cytoplasm with LPP activation. Hypoxia and subsequent reoxygenation are

two stages of the same process associated with abnormal iron metabolism [3,5].

It is believed that the metabolic disorders and/or pathology of a divalent cation accumulation are genetically determined. Thus, in patients with asthma and their sibs, we found a reduction of magnesium and copper levels in blood cells and an increase of calcium ions; a decrease in serum levels of zinc and copper was associated with the T- and B-cell imbalance. Control for the intensity of the free radical process (FRP) is a multi-level system, and an important place in this belongs to the glutathione reductase/glutathione peroxidase antioxidant system (AOS), which carries out the detoxification of hydrogen peroxide using reduced glutathione under the action of glutathione peroxidase (GSH-Px). Fe^{2+}, Cu^{2+}, and Ca^{2+} ions play a significant role in the development of FRP [6]. In our earlier studies, there were no significant differences in the intraerythrocyte non-protein- bound iron (IE-NPBI) level in patients with BPP, depending on the disease nosology, but we found significant variations in the ion content of unclear genesis.

We examined children having bronchopulmonary dysplasia (BPD):

1. Malformations associated with lung hypoplasia entirely or its anatomical structure and tissue elements (n=95; 64±3.4; IE-NPBI variability: 21.1 - 96.8 μmol/10^{12}Er): patients with pulmonary hypoplasia (n=35; 62,6±3,4; IE-NPBI: 25.7-90.8 μmol/10^{12}Er) and cystic pulmonary hypoplasia (n=6; 65.1±11.1; IE-NPBI: 25.7-93.3 μmol/10^{12}Er), patients with Williams-Campbell syndrome (n=11; 57.9±7.0; IE-NPBI: 30.9-96.8 μmol/10^{12}Er), and congenital lobar emphysema (n=13; 58.3±4.6; IE-NPBI: 33.6-92.8 μmol/10^{12}Er);

2. Malformations associated with the presence of excess (additional) units: pulmonary cysts and other congenital tumor formation (n=6;47.8±5.0; IE-NPBI: 28.6-69.8 μmol/10^{12}Er);

3. The unusual location of the anatomical pulmonary structures: patients with Zivert-Kartagener syndrome, a tracheal bronchus and a ciliary dysfunction (n=34; 58.9±3.1; IE-NPBI: 28.3-88.6 μmol/10^{12}Er);

4. The localized violations in the structure of the trachea and bronchi: patients with tracheal and bronchial stenosis, abnormal development of blood and lymph vessels, and varicose veins of the lung (n=11; 68.7±10.7; IE-NPBI: 22.6-112.0 mol/10^{12}Er) .

We also examined patients with the following main diagnoses: cystic fibrosis (CF) (n=69; 58.0±2.7; IE-NPBI: 19.1-117.0 μmol/10^{12}Er), congenital bronchial abnormalities and lung malformations of the undifferentiated type (n=17; 57.5±2.3; IE-NPBI: 27.6-112.0 μmol/10^{12}Er), chronic bronchitis and recurrent obstructive bronchitis (n=21; 63.7±4.0; IE-NPBI: 29.5-99.2 μmol/10^{12}Er), alveolitis (n=20; 57.3±3.7; IE-NPBI: 29.5-89.2 μmol/10^{12}Er), and asthma (n=19; 66.7±5.6; IE-NPBI: 28.5-95.7 μmol/10^{12}Er). In the above data, we took into account only indexes, which were not beyond ± 3σ.

Objective: To examine the relationship between IE-NPBI levels and the severity of the disease, the activity of the antioxidant system, and parameters of RF- tests.

Materials and methods

The study included 230 patients from the above-mentioned group of patients aged between 1 and 17 years. The reference group consisted of 55 apparently healthy children and adolescents of the same age without any BPP. Written informed consent was obtained from patients and their parents. Patients were divided into 4 groups according to IE-NPBI level. Group 1 consisted of 108 patients (51 girls and 57 boys) with conditionally normal IE-NPBI levels (values were close to the reference group); Group 2 consisted of 62 children (33 girls and 29 boys) with a moderate increase in IE-NPBI level; Group 3 consisted of 46 patients (23 girls and 23 boys) with significantly high IE-NPBI level; and Group 4 included 17 children (10 girls and 7 boys)with a reduced IE-NPBI level. Groups were formed in equal manner; the first group consisted 25% of patients with CF, other groups consisted the similar proportional of this diseases; this also apply to other frequency of major pathologies.

Blood was collected into tubes with heparin-lithium; plasma was separated by centrifugation for 15 minutes at 1200 g; the precipitate of RBCs was washed three times with a cold physiological solution. After the last wash, 0.5 mL of the mixed erythrocyte sediment was lysed in 2.0 mL of deionized water; the resulting lysate was frozen and stored at -18°C. After lysate defrosting, hemoglobin and proteins were removed using trichloroacetic acid by slowly adding it to a 5% final concentration; the sample was centrifuged for 30 minutes at 9000 g. In the supernatant, the levels of free (non-protein-bound, but probably in a complex with inorganic substances and amino acids) IE-NPBI, magnesium (IE-NPBM), cuprum (IE-NPBC) and zinc (IE-NPBZ) were determined. The levels of Fe and Mg in plasma and RBC were determined using an automatic Beckmann Coulter Synchron CX-5Δ analyzer. The levels of Cu ions and Zn ions were determined spectrophotometrically using standard «Sentinel» kits. The malone dialdehyde (MDA) content was determined by a reaction with thiobarbituric acid (TBA). GSH-Px activity and total plasma antioxidant status (AOS) were measured using Randox kits on a DU-530 spectrophotometer (Beckmann Coulter, USA). The study of respiratory function (RF) was performed on Masterskrin IOS (Eger, Germany). We recorded at least three flow-volume curves of the forced expiratory volume in 1-second (FEV1) and forced vital capacity (FVC) and then choice the better attempt. In our study, we used the highest values of FEV1 and FVC from the expiratory efforts. Indexes of RF tests were expressed as a percentage of the predicted value. Blood gases and acid-base status was determined in capillary blood from the ear lobe on the device ABL-520 (Radiometer, Denmark).

Statistical analysis was performed using the statistical software "Statistica". For data with normal distribution, inter-group comparisons were performed using student's t-test. The mean (M) and standard deviation (SD) were calculated. A probability value of $P<0.05$ was considered statistically significant. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables.

Results and Discussion

As seen from Table 1, total Fe level in plasma in patients of Groups 1, 2 and 4 were lower than in the reference group. The average content of hemoglobin in the RBCs of all group patients was within the normal range and ranged from 133.1±1.3g/l in Group 1 (minimum content) to 136.5±1.45g/l in Group 3 (maximum content) without statistical significance.

Changes in the levels of other free ions were similar in direction in all groups (Table 1). In Group 1 patients, the level of IE-NPBM was slightly higher than in the reference group; the levels of IE-NPBM in patients of Groups 2 and 3 were significantly higher than in the reference group; however, the level of IE-NPBM in patients of Group 4 was lower than in the reference group. The differences in the IE-NPBM levels between groups were statistically significant. Variations in IE-NPBM level were associated with similar changes in IE-NPBI level. In Group 1 patients, there was a correlation between IE-NPBI level and IE-NPBM level (r=+0.63). Similar abnormalities were marked in GSH-Px activity and the levels of IE-NPBZ and IE-NPBC. In all patients with high levels of IE-NPBI, the GSH-Px activity (in recalculation to 10^{12} RBC) was increased in comparison with the reference group; the maximum activity of this enzyme was observed in Group 3 patients, and minimum activity in Group 4 patients. Only in Group 1 was a moderate correlation between IE-NPBI level and GSH-Px activity (r=-0.36) found. In these patients, there was also a correlation between IE-NPBM level and IE-NPBZ level (r=+0.54). In Groups 2, 3,4, the correlations between IE-NPBM level and IE-NPBI level were less pronounced than in Group 1(r =+0.42, r=+0.43, and r=+0.37, respectively).

In the reference group, *r* rose to +0.55. In Group 3 patients, we noted the following correlations: between IE-NPBM level and IE-NPBZ level (r=+0.81), between IE-NPBI level and IE-NPBZ level (r=+0.39), and between IE-NPBC level and GSH-Px activity (r=+0.4). In the reference group, GSH-Px activity correlated with IE-NPBZ level (r=+ 0.55) and IE-NPBC level (r=-0.46); IE-NPBI level correlated with IE-NPBZ level (r=0.48) and IE-NPBC level (r=-0.42). In almost all patients with BPP, plasma AOS was reduced compared with the conventional norm; the exception was Group 3 patients (with a marked increase in IE-NPBI level). The lowest indexes of plasma AOS were found in patients of Groups 1 and 4. Only in the reference group did we find correlations between IE-NPBI level and AOS level (r=-0.45), as well as between IE-NPBMg level and plasma AOS (r=+0.48) .

Changes in IE-NPBI level were accompanied by certain changes in parameters of RF-tests (Table 2). The most pronounced violations in RF were marked in Group 1, which are characterized by generalized bronchial obstruction and lower FVC. These violations resulted in the pronounced reduction of PaO_2 in the blood. Although hypoxemia occurred in all group patients, the pronounced reduction was marked in Groups 2 and 4 (reduced FEF50 and FEF75), and a slight reduction in FEF50 in Group 3, indicating a patency violation of peripheral bronchi. Mean blood pH was not changed, but there was a base deficit in all groups. The normal rate of base excess (BE) is zero, the permissible limit of variation is ±2.3 mmol/l. The base deficit above this data was observed in Group 3 patients, indicating the metabolic acidosis in these patients. Elimination of carbon dioxide was satisfactory in all groups, but hypercapnia has occurred more often in Group 4.

Table 1.
The relationship between IE-NPBI levels and the levels of IE-NPBM, IE-NPBC and IE-NPBZ, the erythrocyte GSH-Px activity, and total plasma antioxidant status

Parameter	Conditionally normal IE-NPBI level (1)	Moderate increased IE-NPBI level (2)	Significantly high IE-NPBI level (3)	Reduced IE-NPBI level (4)	Reference group (5)
IE-NPBI µM/10^{12} Er	43.9±0.5 $P_{1/2}<0.001$ $P_{1/3}<0.001$	61.7±0.6 $P_{2/3}<0.001$ $P_{/4}<0.001$	89.6±1.8 $P_{3/4}<0.001$	24.9±0.7 $P_{1/4}<0.001$ $P_{4/5}<0.01$	41.9±1.4 $P_{2/5}<0.001$ $P_{3/5}<0.001$
IE-NPBM µM/10^{12} Er	0.35±0.005 $P_{1/2}<0.001$ $P_{1/3}<0.001$	0.43±0.01 $P_{2/3}<0.001$ $p_{2/4}<0.001$	0.50±0.021 $P_{3/4}<0.001$ $P_{3/5}<0.001$	0.28±0.01 $P_{1/4}<0.05$ $P_{4/5}<0.01$	0.32±0.01 $P_{1/5}<0.05$ $P_{2/5}<0.001$
IE-NPBC µM/10^{12} Er	4.07±0.15 $P_{1/3}<0.05$	4.31±0.12	4.75±0.22 $P_{3/4}<0.05$	3.88±0.32	4.28±0.2
IE-NPBZ µM/10^{12} Er	23.3±0.4 $P_{1/2}<0.001$ $P_{1/3}<0.001$	28.9±0.8 $P_{2/3}<0.001$ $P_{2/4}<0.001$	33.2±1.45 $P_{3/4}<0.001$ $P_{3/5}<0.01$	21.1±1.22 $P_{4/5}<0.01$	27.2±1.3 $P_{1/5}<0.05$
GSH-Px U/10^{12} Er	246.8±19.4 $P_{1/3}<0.01$	436.0±43.9 $P_{2/5}=0.05$	491.8±51.0 $P_{3/5}<0.01$	312.5±27.0	274.0±19.9
MDA µM/10^{12} Er	30.9±1.7 $P_{1/4}<0.05$ $P_{1/5}<0.001$	35.2±2.4 $P_{2/4}<0.01$ $P_{2/5}<0.001$	37.2±3.0 $P_{3/4}<0.01$ $P_{3/5}<0.001$	20.6±3.7	17.1±1.3
AOS mM/10^{12} Er	0.868±0.03 $P_{1/5}<0.05$ $P_{1/2}<0.05$	1.03±0.05 $P_{2/3}<0.05$	1.186±0.04 $P_{1/3}<0.001$ $P_{3/4}<0.01$	0.943±0.06	1.09±0.09
NPBI µM/l	14.9±0.02 $P_{1/5}<0.001$	16.9±1.16	18.8±1.18 $P_{1/3}<0.01$	12.5±1.6	17.6±0.9 $P_{4/5}<0.05$

Table 2.
IE-NPBI level and changes in parameters of RF-test

Parameter	Conditionally normal IE-NPBI level (1)	Moderate increased IE-NPBI level (2)	Significantly high IE-NPBI level (3)	Reduced IE-NPBI level (4)
FVC	79.3±2.3	86.8±5.9	86.3±3.5	84.3±8.2
FEV1	75.5±3.1	86.6±6.7	84.6±5.5	85.6±8.9
FEV1/ FVC	94.3±2.2	99.4±2.8	96.6±4.1	101.9±2.1 $P_{1,4}<0.05$
PEFR	78.2±3.1	80.7±6.2	84.2±5.3	88.0±9.7
FEF25	67.4±4.1	76.9±7.5	80.2±7.1	82.3±9.6
FEF50	56.1±3.6	66.4±7.4	73.1±8.4	70.1±10.3
FEF75	45.5±4.0	56.3±7.2	67.8±10.0 $P_{1,3}<0.05$	57.7±7.9
PaO_2 mmHg	71.8±1.6	75.6±3.1	78.7±2.9 $P_{1,3}<0.05$	74.9±3.7
$PaCO_2$ mmHg	33.5±0.8	32.4±1.4	32.8±0.9	36.6±1.7
Hb g/dL	13.1±0.4	12.7±0.3	12.7±0.6	No data
HbO_2,	91.8±0.5	92.1±0.8	93.3±0.4 $P_{1,3}<0.05$	No data
Blood pH	7.4±0.01	7.4±0.01	7.4±0.01	7.4±0.02
BE	-1.92±0.56	-2.2±0.8	-3.6±0.75	-1.6±1.1
Blood SB	23.0±1.0	19.9±1.9	23.4±2.4	23.5±1.0

PEFR- peak expiratory flow rate, SB- sodium bicarbonate, BE- base excess.

In Group 1 patients, the IE-NPBM level moderately correlated with FVC (r=-0.38) and FEF75 (r=-0.4). In Group 2 patients, we found correlations between the plasma iron and FVC (r=+0.43), as well as FEV1(r=+0.51), FEF25 (r=+0.57), FEF50 (r=+0.5), and FEF75 (r=+0.5). In Group 3 patients, we found negative correlations between IE-NPBC level and FVC (r=-0.5), IE-NPBC level and FEV1(r=-0.31), as well as positive correlations between IE-NPBC level and FEF50 (r=+0.42), IE-NPBZ level and FEF50 (r=+0.43); IE-NPBZ level and FEF75 (r=+0.47).

We studied the relationship between IE-NPBI level and the severity of BPP (Table 3). Pulmonary arterial hypertension was detected more frequently in patients of Group 2; however, the pulmonary artery mean pressure was not different in Groups 1–4 and were 0.30±0.01; 0.29±0.01; 0.30±0.01; 0.31±0.02, respectively. Twenty-five percent of patients from Group 4 were infected with mycobacterium tuberculosis and received appropriate therapy, but the Mantoux test remained positive. The largest number of the chronic cor pulmonale cases (37.5%) occurred in Group 4 patients, and these were accompanied by low levels of Fe. Chronic viral and bacterial infections were more common for patients of Groups 3 and 4. In Group 3 patients, in addition to the underlying disease, asthma and atopic dermatitis were diagnosed more often.

Table 3
The frequency of comorbidities (%) among patient groups

Comorbidity	Group 1	Group 2	Group 3	Group 4
	Mean age (yrs)			
	10.4±0.6	9.8±0.7	9.8±0.7	12.5±0.7
PAH	21.7	25.8	15.2	18.8
Forming cor pulmonale	12.0	17.7	10.9	18.8
Chronic cor pulmonale	24.1	16.1	10.9	37.5
CVBI	8.4	5.7	10.8	10.0
Asthma and AD	13.0	12.5	19.6	12.5
CTD	18.5	19.4	23.9	12.5
Tuberculosis	9.4	16.1	21.7	25.0
Chronic hepatitis, cirrhosis	15.7	9.7	10.9	5.9

PAH - Pulmonary arterial hypertension, CVBI - Chronic viral and bacterial infections, AD - Atopic dermatitis, CTD - Connective tissue dysplasia.

It is believed that iron hyperaccumulation is associated with inhibition of the cell cycle, changes in the H+-ATPase activity and the increased oxidative stress [7], which is consistent with our data on the parallel changes in IE-NPBI level and MDA content in Group 3 patients. It is known that the exchange of trace elements varies significantly in the presence of pathology and that cuprum enhances the action of insulin, improves the digestibility of vitamins C and PP, and stimulates glycolysis. In a moderate anaphylactic reaction, cuprum content in the blood increases, but in a severe anaphylactic reaction, the iron level increases [8]. It was found that during an asthmatic attack, the number of •OH ions can be doubled or increased even more. The release of free iron and copper ions from the storage places is simultaneously increased, which leads to the increased production of free radicals and thus increases the risk of asthma attack [9]. This is consistent with our data. In Group 3 patients an increase in the levels of IE-NPBZ, IE-NPBC, and MDA content was accompanied by an increase in the number of children with concomitant diseases such as asthma and atopic dermatitis. We have not found significant differences between the groups of patients with the presence of comorbidities such as chronic pancreatic insufficiency and chronic hepatitis of non-infectious origin. It

was shown that iron deficiency leads to hypoxia with a shift in the acid-base balance in the direction of respiratory alkalosis and metabolic acidosis, an increase in reactive oxygen species generation, suppression of all components of the antioxidant defense system, and the intensification of lipid peroxidation [3,6]. This is consistent with our data on the reduction of GSH-Px activity and AOS reduction in Group 4 patients. In patients with reduced levels of IE-NPBI, close correlations between IE-NPBI level and IE-NPBZ level (r=+0.57), IE-NPBM level and IE-NPBC level (r=+0.5), IE-NPBM level and IE-NPBZ level (r=+0.67), IE-NPBZ level and IE-NPBC level (r=+0.54) were found. GSH-Px activity was correlated with the IE-NPBZ level (r=-0.76) and the IE-NPBC level (r=-0.5). Reducing the iron content limited the proliferation of the iron-dependent bacteria and the intensity of alternative auto-oxidation processes. A decrease in serum iron (in Group 4 patients) in many inflammatory processes coincides with a decrease in the concentration of transferrin and an increase in the concentration of lactoferrin. This leads to the inhibition of hydroxyl radical formation and thereby protects cells from membrane autoperoxidation [10].

Iron is an important component of the cytochromes, and iron deficiency leads to lesions of the epithelial tissue, which is most sensitive to oxygen starvation [8]. In children, the malabsorption of fat, xylose, and a number of other substrates are detected in these conditions. Combination therapy, including beta-carotene (antioxidant supplementation) and iron supplementation, resulted in a significant improvement of the clinical condition compared with untreated patients [11]. In patients of Groups 1–3, MDA content in erythrocytes was higher compared to patients of Groups 4 and 5 (Table 1). In contradistinction to Groups 1–3, we have not found significant activation of LPO processes associated with intracellular iron deficiency, although MDA content was higher in Group 4 than in the reference group. Moreover, in Groups 2 and 3, MDA content was negatively correlated with the superoxide dismutase activity (r=-0.42 and r=0.41, respectively); in Group 4 , we found a positive correlation between MDA content and GSH-Px activity (r=+0.45).

There is evidence that patients with CF (in our study, there were 69 patients evenly distributed by groups) have an imbalance between oxidants and antioxidants, which developed due to various causes [12]. On the one hand, there is a malabsorption of important antioxidants such as vitamin E and carotenoids caused by dysfunction of the gastrointestinal tract; on the other hand, a chronic infection and inflammation in the respiratory system stimulate the synthesis of free radicals by macrophages which have damaging effect [12-15]. Chronic hypoxia maintains the circulation of free radicals in the blood and their fixation in tissues. The concentration of antioxidants in the serum and tissues is reduced with age in CF patients and correlates with the severity of the disease [16]. There is evidence that nitric oxide (NO) is involved in the regulation of iron metabolism; mediators (including NO), which are developed in asthma patients with chronic inflammation, stimulate the increased expression of heme oxygenase (HO). The HO reaction leads to the formation of bilirubin, CO, free iron; this reaction is considered as an antioxidant mechanism. At the same time, free iron is a catalyst for the reactions leading to the formation of active oxygen species (AOS) and thus may contribute to inflammatory processes, closing the vicious circle. Iron metabolism has a certain importance in the biology and pathophysiology of the lower respiratory tract. Iron increases the speed of the NO-synthase reaction [8]. A number of antibiotics and anesthetics have pro-oxidant activity. Other authors in studies with adult CF patients showed that the level of MDA starts falling after intravenous administration of antibiotics and the content of ascorbic acid and α-tocopherol is increased; along with this, the content of lipid hydroperoxides without changing plasma protein oxidation is reduced [14].

Conclusions

In conclusion, results of our study showed that a change in plasma Fe level in patients with BPP is accompanied by similar, but more pronounced, variations in the level of IE-NPBI. The largest number of comorbidities, aggravating the underlying disease, took place in the group of patients with a significant reduction in IE-NPBI level. The pronounced increase in IE-NPBI level was typical for patients with the connective tissue dysplasia, often accompanied by mitral valve prolapse, osteopenia, and mineral metabolism violation. A significant increase in IE-NPBI level, as well as a marked reduction of IE-NPBI level, was an unfavorable factor for the underlying disease. Moderate elevation in IE-NPBI level can be attributed to the compensatory reactions, so in Group 2 patients, there were fewer patients with asthma and atopic dermatitis who underwent surgery on the lungs. The presence of respiratory failure associated with the reduced IE-NPBI levels and lower AOS levels and GP activity may be one of the manifestations of the upcoming decompensation. We found an association between IE-NPBI level and parameters of RF-test in patients with moderate increase in IE-NPBI level (in Group2). An excess of IE-NPBI may indicate a serious disturbance in the activity of the respiratory and redox enzymes in this pathology [7].

Probably, patients with high (toxic) levels of IE-NPBI require the administration of chelating agents, while Group 4 patients require iron supplementation, possibly together with metal chelates to improve its bioavailability; additional courses of antioxidant therapy are suitable for patients of both groups.

Competing interests

The authors declare that they have no competing interests.

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