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COMPREHENSIVE ASSESSMENT OF IMMUNOBIOCHEMICAL MARKERS IN THE DIAGNOSIS OF BRONCHIAL ASTHMA IN COMORBID COURSE WITH TYPE 2 DIABETES MELLITUS

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Abstract
The relevance of this study is обусловлена высокой частотой сочетания bronchial asthma (BA) and type 2 diabetes mellitus (T2DM), which mutually aggravate the clinical course. The aim of the study was to investigate clinical and immunobiochemical markers to improve diagnosis and assess disease severity. A total of 42 patients were examined and divided into two groups: isolated BA and BA combined with T2DM, with comprehensive clinical,

laboratory, and immunological assessments performed. An increase in IL-4 levels up to 30.1 ± 1.4 pg/mL in BA+T2DM compared to BA (24.7 ± 1.2 pg/mL) and a decrease in IFN-γ to 12.3 ± 0.8 pg/mL relative to the control group (18.3 ± 1.0 pg/mL; $p < 0.05$) were observed. Endothelin-1 concentration increased to 2.41 ± 0.12 pg/mL alongside elevated HbA1c levels up to 8.44 ± 0.91%, reflecting endothelial dysfunction and metabolic disturbances. The level of sRAGE decreased to 720.5 ± 150.4 pg/mL in the comorbid group compared to BA (980.3 ± 180.1 pg/mL) and control (1450.3 ± 210.3 pg/mL; $p < 0.05$), indicating enhanced oxidative stress. The obtained results confirm the activation of inflammatory and metabolic pathways in BA combined with T2DM and justify the need for comprehensive laboratory monitoring.

Keywords: Bronchial asthma, type 2 diabetes mellitus, cytokines, endothelin-1, glycated hemoglobin, SRAGE, comorbidity, immunobiochemical markers.

Introduction

Bronchial asthma and type 2 diabetes mellitus are leading chronic noncommunicable diseases, significantly impacting public health and quality of life. According to the World Health Organization (2024), both conditions are highly prevalent and continue to show an upward trend. In recent years, the number of patients with these conditions has increased, driven by shared pathogenetic mechanisms, including metabolic disorders and chronic inflammation. This comorbid condition leads to a more severe clinical picture, increased exacerbation frequency, and a higher risk of adverse outcomes. This necessitates the development of effective approaches to the early diagnosis and management of patients with this comorbidity [2, 6, 12, 15].

The pathogenetic mechanisms underlying the association of asthma and type 2 diabetes mellitus are complex and multifactorial, including disturbances in carbohydrate and lipid metabolism, endothelial dysfunction, and systemic inflammation. Hyperglycemia and insulin resistance trigger the activation of proinflammatory mediators and increased oxidative stress, which contributes to structural changes in the airways and reduces the effectiveness of standard asthma therapy. Chronic inflammation, characteristic of asthma, can negatively impact pancreatic β-cell function and disrupt the regulation of glucose homeostasis. This creates a mutually aggravating pathological process, in which each disease accelerates the progression of the other. Clinically, this manifests as more frequent exacerbations and a reduced therapeutic response [1, 7, 10, 13].

A key link in the pathogenesis of comorbidity is systemic inflammation involving cytokine regulation. Increased production of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β contributes to the development of insulin resistance , endothelial cell activation, and increased bronchial hyperreactivity. Endothelin-1, a vasoactive peptide that serves as an indicator of endothelial dysfunction and vascular remodeling , plays a special role in this process [3, 8, 11, 14]. Studying the interaction between cytokine and endothelial mechanisms

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allows for a more thorough understanding of the pathogenesis of inflammatory and microcirculatory disorders in the combination of bronchial asthma and type 2 diabetes mellitus.

The aim of the study was to study clinical and immunobiochemical markers in patients with bronchial asthma combined with type 2 diabetes mellitus in a comparative aspect in order to optimize early diagnosis and determine prognostic criteria for disease severity.

Materials and methods of research:

The clinical study was conducted at the Aram private clinic in Tashkent. It included 42 patients aged 24 to 65 years, who were being monitored for bronchial asthma (BA). Of these, 15 patients had combined BA and type 2 diabetes mellitus (T2DM), constituting the study group, while 27 patients with isolated BA constituted the comparison group. A control group of 20 relatively healthy individuals, age-matched to those in the study groups, was also formed for immunological studies . The diagnosis of BA was confirmed according to the GINA (Global Initiative for Asthma , 2024), and the diagnosis of T2DM was established in accordance with WHO recommendations (2023).

For clinical evaluation, anamnesis, physical examination, and laboratory and instrumental studies were performed, including general and biochemical blood tests, coagulogram , spirometry with bronchodilator test, chest X-ray, and other standard methods.

As part of the biochemical analysis, the levels of glucose and glycated hemoglobin (HbA1c) were determined .

Immunobiochemical studies included determination of serum concentrations of endothelin-1, IL -4, INFy , and sRAGE cytokines. These were determined by enzyme-linked immunosorbent assay (ELISA) using certified Elisakid (China) and Cytokine (St. Petersburg, Russia) kits.

Statistical data processing was performed using IBM SPSS Statistics , version 26.0. Results are presented as mean ± standard deviation (M±SD). Student's t-test was used to assess intergroup differences; statistical significance was considered at $p < 0.05$.

Research results:

An analysis of the age characteristics of the examined patients demonstrated that the average age of patients with bronchial asthma and type 2 diabetes mellitus was 45.7±1.9 years, which was significantly higher than that of patients with isolated bronchial asthma (36.1±1.4 years, $p < 0.05$). This difference, reaching approximately 1.27 times, reflects the later age of disease onset and progression due to metabolic disorders.

An assessment of the gender distribution revealed that women predominated among patients with bronchial asthma (66.7%), while the proportion of men was 33.3%. In the group with comorbid pathology, a change in this proportion was observed: the proportion of men increased to 40.0%, while that of women decreased to 60.0%. This indicates a relative increase in the frequency of the combined course in men by approximately 1.2 times, which is likely due to the characteristics of the metabolic status and hormonal background that contribute to the development of this pathology.

An analysis of disease duration revealed that in patients with isolated asthma, the average duration was 16.7±1.3 years, while in those with type 2 diabetes mellitus, it was 7.52±0.9 years ($p<0.05$). In patients with comorbid conditions, this indicator was 2.2 times lower, which may indicate a later onset of diabetes in the setting of pre-existing asthma.

A comparative analysis of clinical symptoms revealed more pronounced disease manifestations in patients with comorbidity. The incidence of dyspnea in patients with asthma and type 2 diabetes reached 60.0%, significantly exceeding that in patients with isolated asthma (22.2%; $p < 0.01$). Pale skin and general weakness were recorded in 66.7% of patients with comorbidity versus 44.4% in those with asthma ($p < 0.05$), while cyanosis of the nasolabial triangle and chest pain were more common (13.3% and 20.0%, respectively), reflecting more pronounced hypoxic and vascular disorders.

Of particular significance is the significant increase in the frequency of sweating in patients with a combination of asthma and type 2 diabetes, reaching 86.7%, while in isolated asthma this figure was only 7.41% ($p < 0.001$), indicating severe autonomic dysfunction and metabolic imbalance. At the same time, decreased appetite was more frequently observed in patients with isolated bronchial asthma (48.1%) compared to those with the comorbid form (40.0%), which is likely due to differences in glycemic levels and the degree of insulin resistance (Fig. 1).

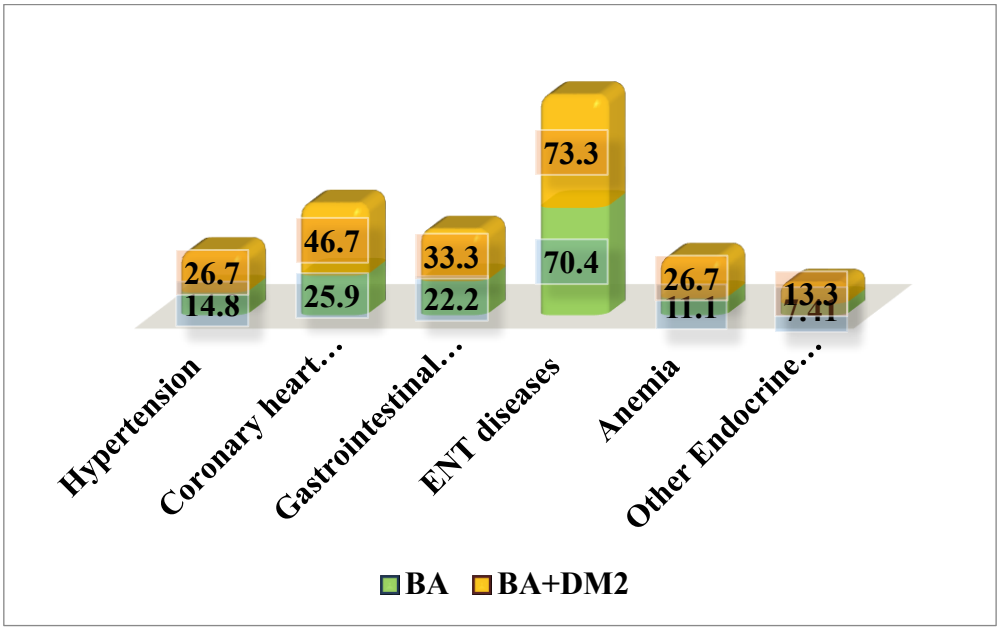


Fig. 1. Concomitant pathology in the examined groups

A comparative analysis of complications revealed that patients with comorbid asthma and type 2 diabetes mellitus had a significantly higher incidence of respiratory failure—53.3% versus 37.0% in those with isolated asthma. A similar trend was observed for pulmonary hypertension (26.7% versus 14.8%, $p < 0.05$), indicating significant damage to the vascular endothelium and impaired microcirculation in the comorbid form of the disease.

The incidence of emphysema in patients with asthma and type 2 diabetes was 13.3%, slightly higher than that in patients with isolated asthma (11.1%). Chronic heart failure was observed

almost 1.8 times more often in patients with this combined pathology (46.7%) compared to patients with asthma without diabetes (25.9%, $p < 0.05$), reflecting the aggravating effect of metabolic disorders on the cardiopulmonary system (Fig. 2).

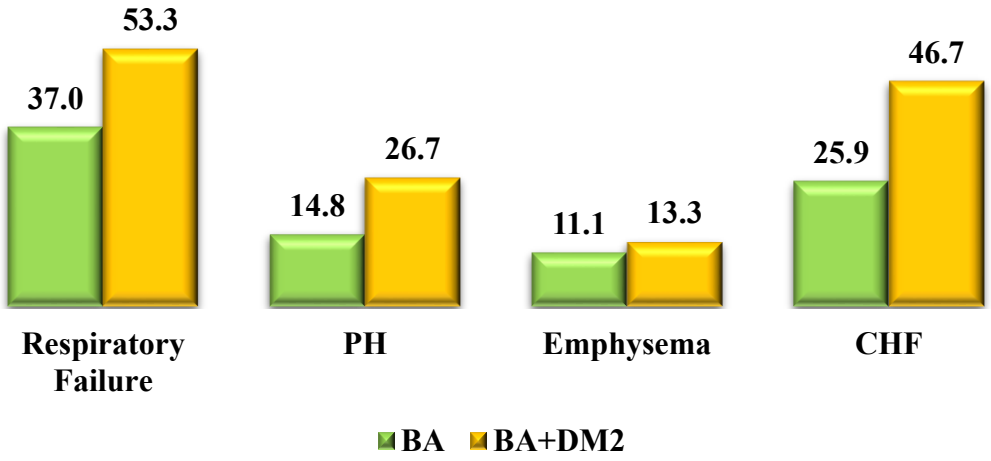


Fig. 2. Analysis of complications in the examined groups, %

A comparative analysis of carbohydrate metabolism parameters revealed significant differences between the study groups. The glycated hemoglobin (HbA1c) level in patients with bronchial asthma was 5.94 ± 0.6%, which was slightly higher compared to the control group (5.31 ± 0.4%). The most pronounced increase was noted in patients with a combined course of bronchial asthma and type 2 diabetes: 8.44 ± 0.91%, which exceeded the control values by almost 1.6 times ($p < 0.05$). This indicates chronic hyperglycemia and impaired protein glycosylation , typical for patients with metabolic disorders. An elevated HbA1c level reflects not only the degree of carbohydrate metabolism compensation, but also an increase in oxidative stress, which contributes to the progression of the inflammatory process in bronchial asthma (Fig. 3).

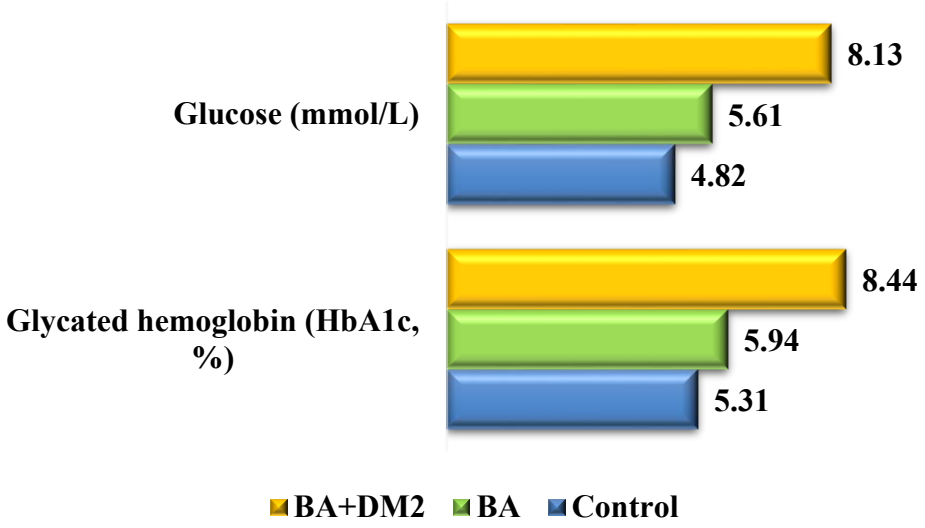


Fig. 3. Parameters of carbohydrate metabolism in the examined groups

Blood glucose levels also showed a statistically significant increase in the patient groups compared to the control group. In isolated bronchial asthma, this indicator was 5.61 ± 0.7 mmol /L, which was moderately higher than the control values (4.82 ± 0.5 mmol /L). In patients with combined pathology, glucose levels reached 8.13 ± 1.27 mmol /L, exceeding the norm by almost 1.7 times ($p < 0.05$). These data confirm a significant impairment of carbohydrate metabolism in patients with bronchial asthma and type 2 diabetes, which increases the metabolic load and promotes the activation of proinflammatory mechanisms.

Given the identified carbohydrate metabolism disturbances and their relationship with the severity of the inflammatory process, a useful step in the study was to examine immunological and biochemical markers. Particular attention was paid to indicators reflecting endothelial function and the cytokine profile. These parameters provide a deeper understanding of the mechanisms underlying the interaction between chronic inflammation and metabolic dysfunction in patients with asthma and type 2 diabetes. Analysis of cytokine levels, including endothelin-1, allows for an objective assessment of the degree of systemic inflammation.

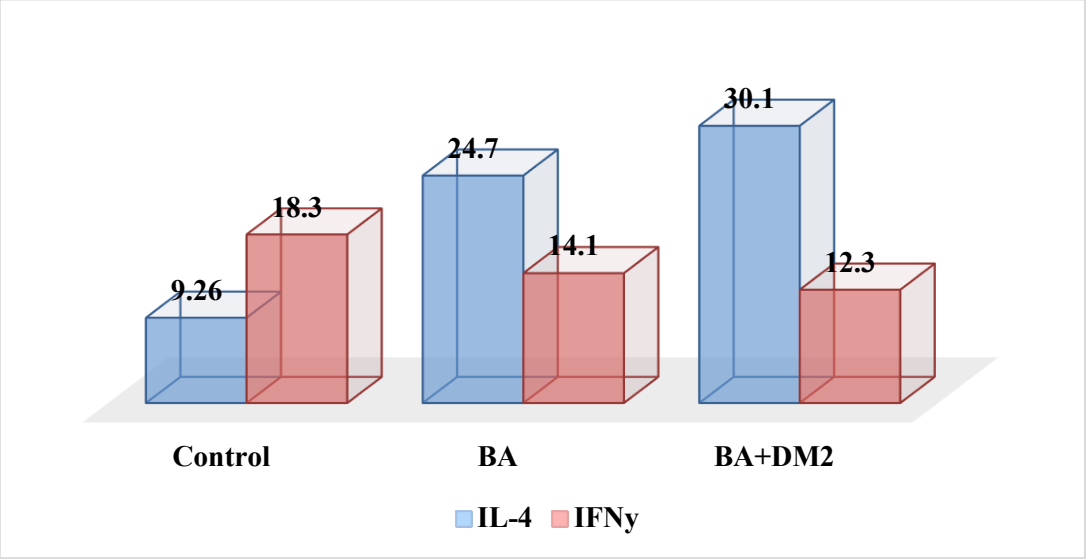
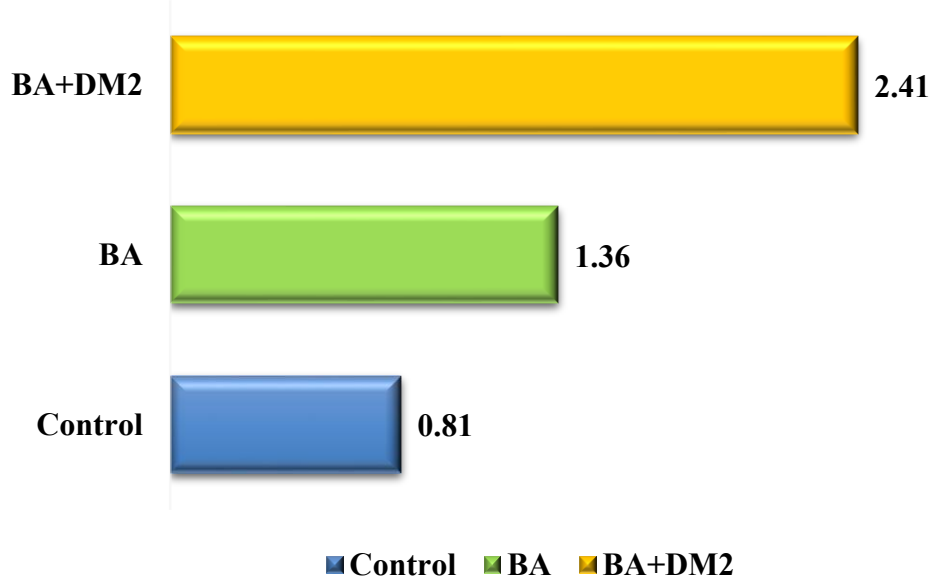


Fig. 4. Cytokine levels in the examined groups, (pg /ml)

In patients with type 2 diabetes mellitus, elevated IL-4 is associated with chronic low-grade inflammation and impaired glucose metabolism through its effect on adipokine balance and insulin resistance . In our study, IL-4 levels were 9.26 ± 0.8 pg /ml in the control group, 24.7 ± 1.2 pg /ml in BA, and 30.1 ± 1.4 pg /ml in patients with combined BA and T2DM. IL-4 levels in BA patients were 2.7-fold higher than control values ($p < 0.01$), and 3.2-fold higher in those with comorbid T2DM ($p < 0.001$). These data reflect increased Th2-dependent inflammation and IL-4 hyperproduction against the background of metabolic disorders, which contributes to the chronic course of the disease and increased airway sensitivity.

In our study, the IFN-γ level was 18.3 ± 1.0 pg / ml in the control, 14.1 ± 0.9 pg / ml in BA and 12.3 ± 0.8 pg / ml in patients with BA + T2DM, which is 1.3 times ($p < 0.05$) and 1.5 times ($p < 0.01$) lower than the control values, respectively (Fig. 4). A decrease in IFN-γ in patients with comorbid pathology reflects the suppression of the Th1 response due to chronic

hyperglycemia and elevated levels of proinflammatory mediators inducing a shift towards a Th2-dominant immune profile. The probable mechanism involves metabolic depletion of T lymphocytes and disruption of the JAK/STAT signaling pathways during hyperinsulinemia , which reduces IFN-γ production and exacerbates allergic airway inflammation. This cytokine imbalance can be considered a key immunobiochemical marker for the comorbid course of bronchial asthma and type 2 diabetes.



Endetolin 1 level in the examined groups (pg /ml)

Endothelin-1 (EN-1) is one of the most potent vasoactive peptides produced by endothelial cells and plays a key role in the regulation of vascular tone, smooth muscle cell proliferation, and inflammatory responses. In asthma, elevated EN-1 levels are associated with the development of endothelial dysfunction and structural changes in the airway vascular wall [5]. In type 2 diabetes mellitus, chronic hyperglycemia and increased oxidative stress promote activation of EDN1 gene expression, leading to increased vasoconstriction and impaired microcirculation. In the present study, it was found that the concentration of EN-1 in the control group was 0.81 ± 0.07 pg / ml, in patients with bronchial asthma it increased to 1.36 ± 0.09 pg / ml, and in the combination of bronchial asthma and type 2 diabetes mellitus it reached 2.41 ± 0.12 pg / ml. Moreover, the level of EN-1 in patients with bronchial asthma exceeded the control values by 1.7 times ($p < 0.01$), while in patients with comorbid pathology it was 3.0 times ($p < 0.001$) (Fig. 5).

The identified changes indicate a progressive impairment of endothelial function as metabolic disorders worsen. A significant increase in EN-1 levels in patients with comorbidities is likely due to the activation of proinflammatory signaling pathways, including NF- κB , as well as increased production of reactive oxygen species, which stimulate endothelin synthesis . An imbalance in the NO/EN-1 system leads to a predominance of vasoconstrictor mechanisms, the development of tissue hypoxia, and increased bronchial vascular remodeling . These processes

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contribute to the progression of bronchial obstruction and a decrease in the effectiveness of therapy.

Table 1 Soluble receptor for advanced glycation end products (pg / mL), (M ± m)

	Control (n=20)	BA (n=27)	BA + T2DM (n=15)
sRAGE (pg / mL)	1450.3 ± 210.3	980.3 ± 180.1	720.5 ± 150.4

A comparative analysis of sRAGE levels demonstrated significant intergroup differences reflecting the pathogenesis of the conditions under study. In the control group, the level was 1450.3 ± 210.3 pg / mL , while in patients with asthma it decreased to 980.3 ± 180.1 pg / mL , which is approximately 1.5 times lower. When asthma was combined with type 2 diabetes mellitus, the sRAGE level decreased even more significantly and reached 720.5 ± 150.4 pg / mL , which is 2 times lower than the control values and 1.36 times lower than the values in the asthma group (table 1) . The identified dynamics indicate a progressive decrease in the protective antioxidant and anti-inflammatory potential of the body. sRAGE is known to function as a "trap" for glycation products , preventing the activation of pro-inflammatory signaling pathways. Its deficiency contributes to increased AGE-RAGE interactions, activation of oxidative stress and chronic inflammation.

Discussion of the obtained results

The conducted analysis revealed that the average age of patients with comorbid bronchial asthma (BA) and type 2 diabetes mellitus (T2DM) was statistically significantly higher compared to patients with isolated bronchial asthma, which is consistent with the literature data indicating the age-dependent nature of metabolic disorders and a later onset of combined pathology (Pan et al ., 2025). When analyzing the gender composition, a relative increase in the proportion of men among patients with asthma and type 2 diabetes was noted, which is consistent with epidemiological studies demonstrating a higher predisposition of males to metabolic stress and vascular disorders (Fuseini et al ., 2017). The average duration of the disease in patients with comorbid asthma was 2.2 times shorter than in isolated asthma, which may reflect a more rapid progression of the pathological process in the context of impaired metabolism. Clinical symptoms in this category of patients were more pronounced: shortness of breath, weakness, sweating, and signs of tissue hypoxia were observed more often, indicating a systemic nature of inflammatory-metabolic disorders. The incidence of complications such as respiratory failure, pulmonary hypertension, and chronic heart failure was significantly higher in patients with a combination of asthma and type 2 diabetes, which is consistent with modern concepts of the synergistic effect of inflammation and endothelial dysfunction on the cardiopulmonary system (Howell et al ., 2023).

Laboratory analysis revealed significant disturbances in carbohydrate metabolism: glycated hemoglobin (HbA1c) and blood glucose levels were significantly higher in patients with asthma and type 2 diabetes, indicating decompensation of metabolic processes and activation

of proinflammatory cascades. Changes in the cytokine profile were characterized by a significant increase in IL-4 concentrations and a decrease in IFN-γ, reflecting a shift in the immune response toward Th2-dominant inflammation; similar results were obtained in studies by Lama. et al . (2017). Furthermore, elevated endothelin-1 (EN-1) levels in patients with comorbidity confirm the presence of severe endothelial dysfunction induced by hyperglycemia and oxidative stress. The combination of these changes reflects the integrative interaction of immune, metabolic, and vascular factors that contribute to the severe course of the disease in patients with comorbidity of asthma and T2DM.

sRAGE values obtained in the study (1450.3 ± 210.3 pg / mL in the control; 980.3 ± 180.1 pg / mL in BA; 720.5 ± 150.4 pg / mL in BA + T2DM) are generally consistent with the data presented in the modern literature and confirm the pattern of a decrease in this marker in inflammatory and metabolic diseases. Thus, in the study of El-Seify MYH et al ., the sRAGE level in patients with bronchial asthma was about 899 ± 399 pg / mL versus 1406 ± 474 pg / mL in the control group, which is comparable with our results. Similar trends are described in the work of Sukkar MB, where a significant decrease in sRAGE was noted in the neutrophilic phenotype of asthma associated with a more severe course of the disease. More recent studies, including the work of Hu H, have also shown reduced sRAGE concentrations in asthmatic patients compared to healthy individuals, confirming the universality of this pattern.

in sRAGE found in patients with a combination of bronchial asthma and type 2 diabetes mellitus (720.5 ± 150.4 pg / mL) goes beyond the values typical for isolated asthma and indicates the additional influence of metabolic disorders. The obtained data are consistent with the concept of activation of the AGE-RAGE signaling pathway in hyperglycemia, which is widely described in diabetes studies. Studies devoted to metabolic diseases have also shown that a decrease in sRAGE is associated with increased oxidative stress, endothelial dysfunction, and chronic inflammation. Thus,

Conclusion

Thus, patients with comorbid asthma and type 2 diabetes mellitus exhibited a more severe clinical and laboratory course of the disease, accompanied by significant carbohydrate metabolism disorders, endothelial dysfunction, and immune imbalance. These data confirm that metabolic disturbances exacerbate chronic airway inflammation and contribute to the development of vascular complications. Increased IL-4 and endothelin-1 levels, coupled with decreased IFN-γ, reflect Th2 activation and weakened anti-inflammatory control. These relationships highlight the need for a comprehensive approach to the diagnosis and treatment of comorbid conditions, taking into account metabolic and immunological characteristics. Incorporating these markers into monitoring patients with asthma and type 2 diabetes mellitus will optimize risk stratification and improve the effectiveness of personalized therapy. A comparison of our own data with the results of other authors confirms that a decrease in sRAGE levels is a universal pathogenetic marker, and its more pronounced decrease in comorbid pathology reflects the synergistic effect of bronchial asthma and type 2 diabetes mellitus on inflammatory and metabolic processes.

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