UDC 616.379-008.64+616.248-07-053.2+576.08+616-097
DOI: 10.56871/CmN-W.2024.86.73.004

# TYPE 1 DIABETES AND BRONCHIAL ASTHMA IN CHILDREN: INTERRELATION AND MUTUAL INFLUENCE. SCIENTIFIC REVIEW

**© Egor S. Afonin, Iana I. Balakhonova, Rustam B. Bolatov, Otman Taj, Artysh M. Shozhukpan, Anna S. Kapustina, Tamara V. Kosenkova**

V.A. Almazov National Medical Research Center. 2 Akkuratov str., Saint-Petersburg 197341 Russian Federation

**Contact information:**
Tamara V. Kosenkova — Doctor of Medical Sciences, Professor; Professor of the Department of Pediatric Diseases with the Clinic. E-mail: tamara.kosenkova1955@gmail.com ORCID: https://orcid.org/0000-0002-6022-3420 SPIN: 3719-3172

***For citation:*** Afonin ES, Balakhonova IaI, Bolatov RB, Taj O, Shozhukpan AM, Kapustina AS, Kosenkova TV. Type 1 diabetes and bronchial asthma in children: interrelation and mutual influence. Scientific review. Children's Medicine of the North-West. 2024;12(2):45–66. DOI: https://doi.org/10.56871/CmN-W.2024.86.73.004

**Received: 12.12.2023** **Revised: 14.02.2024** **Accepted: 05.06.2024**

**Abstract.** The aim of this scientific review is to systematize and analyze the literature on the epidemiology, pathogenesis, clinical manifestations, and treatment of children with comorbid pathologies — bronchial asthma combined with type 1 diabetes mellitus — in the context of comorbidity or the diseases' independence/antimorbidity. The study demonstrated that the relationship between type 1 diabetes mellitus (T1DM) and bronchial asthma (BA) is much deeper and more complex than previously thought under the Th1/Th2 paradigm. Allergic and autoimmune diseases are considered comorbid pathologies that are closely interlinked, affecting the onset, sequence of clinical symptoms, nature of control, and specificity of each other's therapy. Scientific data indicate the existence of a common complex polygenic basis for the development of both conditions. Genetic differences may play a crucial role in the relationship between type 1 diabetes and bronchial asthma, but further research in this area is needed. Current understanding of potential pathogenetic and immunological triggers playing key roles in the onset, progression, and treatment of the combined T1DM+BA condition can be conceptualized as a tripartite interaction of genetic factors, environmental conditions, and a unique cytokine profile in these patients. The multifactorial connection should now be considered bidirectional by nature, with each element of this system impacting the others without a clear sequential order. The pathogenesis of the combined pathology (T1DM+BA) is based on immune dysregulation with a cytokine imbalance (a reduction in the number and depletion of reserve capacities of T-reg cells, as well as a defect in the suppressive mechanism of IL-10). This results in the emergence or intensification of the inflammatory process, an imbalance in autoimmunity mechanisms, further disrupting immune homeostasis and leading to the development and progression of symptoms in both BA and T1DM.

**Keywords:** *children, bronchial asthma, type 1 diabetes mellitus*

# САХАРНЫЙ ДИАБЕТ 1-го ТИПА И БРОНХИАЛЬНАЯ АСТМА У ДЕТЕЙ: ВЗАИМОСВЯЗЬ И ВЗАИМОВЛИЯНИЕ. НАУЧНЫЙ ОБЗОР

**© Егор Сергеевич Афонин, Яна Игоревна Балахонова, Рустам Болатович Болатов, Отман Тадж, Артыш Мирославович Шожукпан, Анна Сергеевна Капустина, Тамара Васильевна Косенкова**

Национальный медицинский исследовательский центр им. В.А. Алмазова. 197341, г. Санкт-Петербург, ул. Аккуратова, 2

**Контактная информация:**
Тамара Васильевна Косенкова — д.м.н., профессор; профессор кафедры детских болезней с клиникой. E-mail: tamara.kosenkova1955@gmail.com ORCID: https://orcid.org/0000-0002-6022-3420 SPIN: 3719-3172

***Для цитирования:*** Афонин Е.С., Балахонова Я.И., Болатов Р.Б., Тадж О., Шожукпан А.М., Капустина А.С., Косенкова Т.В. Сахарный диабет 1-го типа и бронхиальная астма у детей: взаимосвязь и взаимовлияние. Научный обзор // Children's Medicine of the North-West. 2024. Т. 12. № 2. С. 45–66. DOI: https://doi.org/10.56871/CmN-W.2024.86.73.004

**Поступила: 12.12.2023** **Одобрена: 14.02.2024** **Принята к печати: 05.06.2024**

**Резюме.** Цель научного обзора — систематизация и анализ имеющихся в литературе данных по эпидемиологии, патогенезу, клинической картине, а также терапии детей с сочетанной патологией: бронхиальная

астма + сахарный диабет 1-го типа пациентов в контексте коморбидности или самостоятельности/антиморбидности данных заболеваний. В результате проведенного исследования показано, что связь между сахарным диабетом 1-го типа (СД1) и бронхиальной астмой (БА) намного глубже и сложнее, чем существовавшая ранее парадигма Th1/Th2. При этом аллергические и аутоиммунные заболевания являются коморбидной патологией, тесно взаимосвязаны, оказывают влияние на дебют, последовательность возникновения клинических симптомов, характер контроля и особенность терапии друг друга. Научные данные свидетельствуют о существовании общей сложной полигенной основы формирования СД1 и БА. Возможно, именно генетические различия могут иметь решающее значение во взаимоотношениях сахарного диабета 1-го типа и бронхиальной астмы, но исследования в этом направлении должны быть продолжены. И поэтому современное представление о потенциальных патогенетических и иммунологических триггерах, играющих решающую роль в дебюте, течении и терапии сочетания БА+СД1, можно представить в виде тройственного взаимоотношения *генетических факторов, окружающей среды и уникального цитокинового профиля* у данных пациентов. Многофакторную связь в настоящее время следует рассматривать как двунаправленную по своей природе. При этом каждый элемент этой системы влияет на другие без четкого последовательного порядка возникновения. В основе патогенеза сочетанной патологии (СД1+БА) лежит иммунная дисрегуляция с цитокиновым дисбалансом (снижение количества и истощение резервных возможностей T-reg клеток, а также дефект подавляющего механизма IL-10). Следствием этого является появление/усиление воспалительного процесса, разбалансировка механизмов аутоиммунитета, что сопровождается еще большим нарушением иммунного гомеостаза и формированием/прогрессированием симптомов как БА, так и СД1.

**Ключевые слова:** *дети, бронхиальная астма, сахарный диабет 1-го типа*

## INTRODUCTION

The relationship between autoimmune and atopic diseases is a subject of scientific interest and close attention of scientists all over the world, especially in recent decades due to the widespread and steady increase in the number of patients not only with bronchial asthma (BA) but also with type 1 diabetes mellitus (T1DM) [1].

BA is a heterogeneous disease manifested by different phenotypes and characterized by chronic airway inflammation, the presence of respiratory symptoms (wheezing, dyspnea, chest congestion and cough) that vary in time and intensity and manifest with variable airway obstruction [2]. BA occupies the leading place among chronic respiratory diseases in children. Both in Russia and abroad there is not only an increase in children suffering from BA [2, 3], but also a shift of the disease debut to an early age (2–3 years of life). And if in the second half of the XX century, the incidence was higher in children living in more prosperous countries, then recently the trend of BA growth has been registered in developing countries [4]. As it is known, the pathogenesis of BA is quite complex and associated with a complex influence of both *internal* (genetic predisposition to atopy and bronchial hyperresponsiveness, gender, obesity) and *external factors* (food, household — house dust mites, cockroaches; epidermal — animal allergens; fungal allergens, plant pollen and other air pollutants, such as ozone, sulfur and nitrogen dioxides, diesel combustion products, tobacco smoke, active and passive smoking; infectious agents — mainly respiratory viruses; diet — increased consumption of highly processed foods, increased intake of omega-6 polyunsaturated fatty acid and decreased intake of antioxidants in the form of fruits and vegetables and omega-3 polyunsaturated fatty acid in fatty fish; occupational hazards [2, 3, 5–7].

In the pediatric population, in parallel with the increase in allergic respiratory diseases, there has been a significant increase in autoimmune disorders, the main one is T1DM [1]. It is a multifactorial chronic pathology, caused by cell-mediated immune destruction of the pancreas as a result of a complex interaction between genes and environmental factors, when chronic insulitis leads to T-lymphocyte destruction of β-cells with subsequent development of absolute insulin deficiency [8]. In most countries, including the Russian Federation, an increasing incidence of T1DM in childhood is registered. The prevalence of T1DM is 22.9 new cases per year per 100,000 children under 15 years of age [9] and number of such cases is increasing by approximately 3–5% per year [10–12]. In meta-analysis, M. Mobasseri et al. [13] showed not only a steady increase in the incidence of T1DM in the last decade worldwide (the incidence of T1DM was 15 per 100,000 people, and the prevalence was 9.5 per 10,000 people), but also the existence of differences in the incidence of T1DM in children in different geographical regions and ethnic and racial distribution. Very high incidence

(greater than or equal to 20 per 100,000 per year) was in Sardinia, Finland, Sweden, Norway, Portugal, UK, Canada and New Zealand and low incidence (less than 5 per 100,000 per year) was in China, Japan and Rwanda [14]. The incidence of T1DM increased with age, with maximum in children 10–14 years of age [14].

Scientists all over the world have noted that in recent decades there has been a steady increase in the number of patients with a combination of atopic and autoimmune diseases, including BA and T1DM. However, there are few articles devoted to the study of pathogenetic aspects of molecular genetics and cell-receptor mechanisms of its development and manifestation, peculiarities of the clinical debut, interrelation/interaction, comorbidity or antimorbidity of the combined pathology. But this knowledge is quite contradictory (from statistically significant evidence of inverse association between autoimmunity and one or more atopic diseases to confirmation of positive association) [15–18].

At the same time, every attempt to understand this situation raises new and new questions concerning the interaction/interrelation/influence of autoimmune and atopic mechanisms in the genesis of T1DM and BA, since the presence of two such serious chronic diseases in one child requires not only a careful selection of therapy, but, for example, aimed at preventing the formation of complications.

## AIM

Therefore, the aim of this review was to systematize the data available in the literature concerning the epidemiology, pathogenesis, clinical features and therapy of patients suffering from the combined pathology of BA and T1DM in the context of comorbidity or independence/antimorbidity of such diseases.

## TH1/TH2 PARADIGM

It is well known that BA and T1DM belong to chronic inflammatory diseases. However, the pathogenesis of each nosology is based on the involvement of opposite branches of the adaptive immune system [15, 19], synthesizing different subpopulations of CD4+ T-helper cells of types 1 and 2. Two ways mediate reactions of cellular immune response (Th1) proceeding by the mechanism of chronic inflammation, or reactions of humoral immune response associated with the production of antibodies (Th2). The main cytokines of the Th1 immune response underlying autoimmune pathology are *pro-inflammatory cytokines*: interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), while in Th2 immune response, which leads to IgE-mediated (atopic) diseases (BA), are *anti-inflammatory cytokines*: IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and transforming growth factor-β (TGF-β) [15, 19–21]. The difference in cytokine secretion between Th1- and Th2-immune response cells leads to functional differences, because Th1 cells, producing IFN-γ, activate CD8+ T-lymphocytes and macrophages and promote cellular immunity, while Th2 cells stimulate the synthesis of IgM, IgG1 and IgE and activate eosinophils, contributing to the development of atopy through activation of IL-4 and IL-5 synthesis [22]. At the same time, IL-4 and IL-10, the exclusive products of Th2-immune response, inhibit IL-2-mediated Th1-immune responses and suppress the production of pro-inflammatory cytokines [23]. And therefore, scientists suggested that Th1 cytokines play a direct role in the pathogenesis and progression of T1DM, while Th2 cytokines should provide protection against Th1-mediated destruction of β-islet cells. For this reason, for almost three decades, there has been a hypothesis based on the assumption that diseases mediated by Th1- and Th2-immune responses should be mutually exclusive, because the expansion of Th1 clones in individuals with T1DM should lead to a reduction of Th2 clones, thus preventing the development of atopic diseases and vice versa [24–30]. Consequently, autoimmune (associated with Th1–1) and allergic (associated with Th1-immune response) diseases would be mutually exclusive [29–32].

This concept is supported by a number of comparative studies on epidemiology. It was shown that patients with T1DM have a lower incidence of BA than controls [33]. The authors considered, one of the factors explaining the negative association between T1DM and BA is an increase in the level of glucocorticosteroids with anti-inflammatory effect in patients with BA [34]. Consequently, according to scientists, the presence of T1DM reduces the risk of manifestation of atopic diseases. Also, a retrospective cohort non-comparative study of the incidence of BA in 7230 children with T1DM hospitalized at the Morozov City Children's Clinical Hospital (MCCH) between 2003 and 2012 showed that the incidence of BA in patients with T1DM was 0.86%, which is significantly lower than the population data. This fact may be an indirect

confirmation of the Th1/Th2 concept of immunopathogenesis of T1DM and atopic diseases [35]. M.A. Toska et al. [36] evaluated lung function in 20 children with a combination of T1DM and allergic rhinitis (AR) and in 59 controls suffering only from AR. Scientists found that children with AR had a significant increase in forced expiratory flow rate (by 25 and 75% of forced vital capacity) after bronchodilation compared to the group of children with a combination of T1T1DM and AR. This result may indicate a possible protective role of T1DM associated with AR in the development of BA. In meta-analysis of 25 studies from Europe and North America, C.R. Cardwell et al. [37] described a decreased incidence of BA in children with T1DM (OR 0.82; 95% CI 0.68–0.99; p=0.04). Also in other study, H.O. Mirghani et al. [38] showed a potential protective role of T1DM in relation to the development of atopic dermatitis (AD) (OR 0.69; 95% CI 0.67–0.72). J.P. Krischer et al. [39] found that in children with the first-degree relative who had T1DM, the occurrence of islet cell antibodies (ICA), as the first autoantibodies associated with T1DM, reduced the subsequent risk of BA, AR, and AD, and a presence of autoantibodies to insulin (Anti-insulin IgG) or glutamate decarboxylase (GADA) — atopic dermatitis [39]. Several studies [29–32] have also shown that the occurrence of BA and allergic respiratory symptoms is reduced in patients with T1DM. This protection may extend to siblings of probands without T1DM [25]. But, according to the authors, this, firstly, suggests an effect mediated by a common genetic background, and secondly, by exposure to the same environmental factors during pregnancy or early life [25].

Thus, for more than two decades, the Th1/Th2 paradigm has supported the theory of immune system polarization. Internal and external factors acting together initiate either a Th1-immune response, which through the release of pro-inflammatory cytokines (IFN-γ, IL-2, lymphotoxin-α and others) causes activation of macrophages, increases cellular cytotoxicity and so on, or Th2, which is mediated by anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13, etc.) and leads to the activation of eosinophils as well as induction of antibody formation, including IgE. And thereby determining the balance between two different inflammatory patterns [9].

## "HYGIENE HYPOTHESIS" AND OTHER FACTORS

Despite the large number of scientific data and some success in the study of pathogenesis of both T1DM and BA, there is currently opposite data on the interrelated course of these diseases. Among the published works, there are studies both confirming relationship and pointing to genetic, immunologic, and environmental factors contributing to the antimorbidity of the pathologies [41, 42]. A retrospective cohort study was conducted from 1998 to 2011 with use of data from the Taiwan National Health Insurance System. The research included 3,545 children younger than 8 years of age (55.1% girls and 26.5% boys) with T1DM and 14,180 control. It was shown that children with T1DM had a 47% higher incidence of BA (6.49 vs. 4.42 per 1,000 persons, respectively) and an adjusted risk ratio (HR) of 1.34 (95% CI [CI]¼ 1.11–1.62). Meanwhile, patients with T1DM, hospitalized more than twice at emergency department because of diabetes, had a 2-fold higher adjusted risk (HR) of development of BA, which was 38.6 (95% CI 28.5–52.2) versus 17.4 (95% CI 12.9–23.6). Consequently, according to the authors, children with T1DM had significantly higher incidence of bronchial asthma than controls, and the absence of T1DM compensation increased the risk of its formation [43].

M.H. Black et al. [44], as well as Y.T. Hsiao et al. [43], showed a higher prevalence of BA in adolescents with T1DM (10.8%) compared to the general population (8.7%). Also authors found that young people with T1DM, who had the highest number of visits to emergency department or frequent hospitalizations for T1DM, were characterized by a higher risk of development of BA. S. Klamt et al. [45], as well as H. Villa-Nova et al. [46] demonstrated that children with T1DM more often had manifestations of IgE-mediated allergies (allergic rhinitis, urticaria and BA), as well as sensitization to allergens compared to controls without diabetes, which, according to J. Kero et al. may be explained by the coexistence of Th1 and Th2-dependent pathologies. The authors hypothesized a common environmental trigger for both diseases [47], which may influence the susceptibility of patients to BA and T1DM [48].

In the studies, D. Strachan [49], P.I. Pfefferle et al. [50] found that children living with several older siblings, especially in the same bedroom [51], or attending kindergarten before 1 year of age have a lower risk of forming allergic diseases [50] and T1DM [14] than children attending kindergarten over 2 years of age and children from small families. A child's life on a farm, associated with early contact with farm animals, also plays a protective role in the formation of T1DM [52].

According to other authors, the improvement of living conditions in developed countries has led to a decrease in parasitic infections, which may correlate with an increase in the frequency of immune-mediated disorders. At the same time, a number of researchers have pointed out the role of parasitic infections in the formation of autoimmune and atopic pathology in children [53, 54]. They demonstrated that helminths can prevent the development of such diseases by inducing an increase in Th2 cytokines and reducing the secretion of cytokines associated with the Th1/Th17-immune response [55]. Helminths promote the synthesis of gastrointestinal mucosa by synthesis of FhHDM (*Fasciola hepatica*) and *omega-1 (S. mansoni)* [56], which are defense molecules of helminth and possibly play an important role in atopic and autoimmune diseases. Due to the lack of research, the association of atopic and autoimmune diseases with the presence of helminths in the body is controversial.

K.E. Fujimura et al. [57] found that the composition of gut microbiota in infants of the first month of life is crucial for the development of the immune system, so any changes during this period can cause irreversible changes in this. Thus, the microbiota in children at high risk of development T1DM or BA is characterized by common taxonomic features: low phylum biodiversity [18, 58], higher *Bacteroides/Firmicutes* ratio, relative abundance of *Clostridium* and relative deficiency of *Lactobacillus* and *Bifidobacterium* [18, 59]. Many authors believe that this phenomenon may be based on the increased production of short-chain fatty acids (SCFAs) by bacteria (acetate, butyrate, and propionate), as they are involved in the regulation of both innate and adaptive immune systems via the G-protein-coupled receptor (GPR43) [60]. Thus, acetate reduces the number of autoreactive T cells, butyrate promotes the differentiation and activation of Treg cells [61]. Components inhibit the expression of class I genes of the major histocompatibility complex (MHC) and stimulate proteins on B-lymphocytes, promote the differentiation of B cells into plasma cells and memory cells that produce specific IgG and IgA [62]. Meanwhile, acetate and propionate increase insulin sensitivity, and butyrate maintains the integrity of the intestinal epithelium [63]. The findings were confirmed in an experimental study in non-obese mice with T1DM by supplementation with butyrate and acetate, which had a protective effect, reducing the incidence of autoimmune diabetes or delaying its onset [64]. In addition, mice with defective production of GPR43 or SCFAs showed a stronger inflammatory response with high production of pro-inflammatory cytokines after exposure to conventional aeroallergens [65]. However, the mechanism of tolerance is maintained through a complex network of interactions between several cell types (T- and B-lymphocytes, DCs and others). At the same time, excessive migration of DCs can lead to its abnormal activation, imbalance of immune response, which contributes to autoimmune manifestations, infectious and allergic diseases [66]. Chronic inflammation can also induce the formation of neoepitopes that avoid central tolerance and thus promote the formation of autoantigens with massive activation of autoreactive T lymphocytes [67]. At the same time, gut dysbiosis in the presence of reduced microbiota diversity, which is characteristic of many chronic non-infectious diseases, plays a crucial role in tolerance disorders and underlies the genetic predisposition to the development of atopic and autoimmune diseases (*HLA-haplotypes*, genes encoding cytokines or their receptors) [68, 69].

Metsala et al. [70] in nationwide cohort study, included Finnish children under 16 years of age born between January 1, 1981, and December 31, 2008 who had BA (n=81,473) or T1DM (n=9541) by the end of 2009, a 10% random sample from each birth year cohort (n=171,138) was selected as the reference group. Children were identified from the Central Register of Medicines maintained by the Finnish Social Insurance Administration. Authors studied the association between BA and T1DM using a multiple-condition modeling approach to estimate the rate of transition between health and disease from birth. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to represent the change in the rate of transition between both diseases. The authors found that when adjusted for sex and decade of birth, a pre-existing diagnosis of T1DM reduced the risk of subsequent BA by 18% (95% CI 0.69–0.98), and a pre-existing diagnosis of BA increased the risk of subsequent T1DM by 41% (95% CI 1.28–1.54). These results could not be explained by the presence of maternal BA/T1MD or birth-related factors. The authors suggested that the association between these diseases is more complex than previously thought, and its direction may depend on the sequence of disease onset (T1DM in children with BA or BA in children with T1DM) [70].

Also, A.I. Smew et al. [71], in cohort study, investigated the bidirectional association between BA and T1DM and possibility of a shared risk of these diseases. It was made by investigating familial coaggregation model. The study included 1,347,901 children, who were born between January 1, 2001 and December 31, 2013. The data was obtained from several Swedish national registries. All children were born to singleton pregnancies. Cases of BA and T1DM were defined using a combination of diagnoses and drug prescriptions: 121,809 children (9.5%) were diagnosed with BA, 3812 children (0.3%) had T1DM, and 494 children were with a combination of BA and T1DM (0.4% of all BA cases or 13% of all T1DM cases). The authors noted the association between BA and T1DM (OR 1.15; 95% CI 1.05–1.27). Children with BA had increased risk of development of T1DM later in life (OR 1.16; 95% CI 1.06–1.27), but the subsequent risk of development of BA was not significantly different among children with T1DM (OR 0.92; 95% CI 0.75–1.12). Siblings of children with BA were at increased risk of development of T1DM (OR 1.27; 95% CI 1.13–1.42) and vice versa. Results remained positive after controlling for a direct association of one disease with the other. Consequently, the authors' findings suggest the possibility of co-occurrence and coaggregation of BA and T1DM in children, their siblings and, in addition, may indicate common familial factors contributing to the comorbidity of the two diseases [71]. Hyun D. Yun et al. [72], and Zeng et al. [73], in meta-analysis, showed that BA was associated with an increased risk of development of T1DM (OR 2.11; 95% CI 1.43–3.13; p <0.001 and OR 1.15; 95% CI 1.06–1.25, respectively).

J. Xie et al. [74], conducted meta-analysis with use of three databases (PubMed, Embase, and Web of Science) from their inception to February 1, 2021. They studied the presence of bidirectional causality between BA and T1DM based on the calculation of pooled hazard ratios (HR), odds ratio (OR), 95% confidence interval, and full genomic studies (FinnGen). Weighted inverse variance (IVW), weighted median, and MR-Egger methods were used to estimate causal effects. MR-Egger regression and residual sum MR-pleiotropy, an outlier test were performed to assess robustness and horizontal pleiotropy. According to data, BA in children was associated with an increased risk of T1DM (OR 1.30; 95% CI 1.05–1.61; p=0.014), whereas T1DM was not associated with risk of BA (OR 0.98; 95% CI 0.64–1.51; p=0.941; OR 0.84; 95% CI 0.65–1.08; p=0.168). Analysis of variance showed an increased genetic risk of T1DM in children with BA (OR 1.308; 95% CI 1.030–1.661; p=0.028). IVW analysis showed no association between T1DM and genetic risk of BA (OR 1.027; 95% CI 0.970–1.089; p=0.358). Based on their research, the authors concluded that BA in children is a risk factor for the development of T1DM. There is no epidemiologic or genetic evidence of an association of T1DM with the incidence of BA [74].

P. Fsadni et al. [75], compared the registered incidence of T1DM with the prevalence of atopic diseases, and found that T1DM has a positive correlation with both recurrent wheezing and BA. And L.C. Stene et al. [48], analyzing epidemiological data, showed a strong positive association between T1DM and BA and suggested the presence of common environmental factors that may influence the predisposition to both diseases. At the same time, a multicenter case-control study EURODIAB Study 2 Study Group in children proved a negative association of T1DM with BA, BA and rhinoconjunctivitis, respectively [76].

J. Wahlberg et al. [77], included in their study 7208 Swedish children and showed a relationship between the presence of wheezing associated with BA in the first year of life and subsequent appearance of autoantibodies to GADA and antibodies to pancreatic β-cell tyrosine phosphatase (IA-2A) at the age of 2.5 years. In addition, the authors found that allergic rash at multiple sites, recurrent at least three times within 12 months, and symptoms due to sensitization to animal allergens were associated with the risk of IA-2A. Food allergies to egg, cow's milk, fish, nuts/mineral (monovalent or in combination) were associated with risk of formation of GADA and IA-2A. The researchers concluded that allergic symptoms in young children are associated with the appearance of autoantibodies which formed due to T1DM in the first years of life. This fact also confirms the relationship of these diseases [77].

## GENETIC HYPOTHESIS

Genetic studies have shown that there are genes involved in the development of both BA and T1DM *(CTLA-4* (lymphocyte-associated protein 4) and *HLA-DQB1 0201/DQB1 0302)*. In this case, N. Taleb et al. [30] found an association, but not statistically significant, between the G-allele in the 49th (A/G) nucleotide of the *CTLA-4* gene and increase in symptoms of BA, as well as a higher risk of development of T1DM [30, 78]. According

to the authors, *CTLA-4* polymorphisms may represent a common genetic risk for both diseases [79]. A study of *HLA-DQB1* alleles showed a higher frequency of *HLA-DQB1* 0201 in children with BA and a higher frequency of *HLA-DQB1* 0301 in healthy people [80]. At the same time, *HLA-DQB1* 0201 carriers and T1DM sufferers were characterized by significantly fewer symptoms of BA compared to patients with T1DM but not carriers of the *HLA-DQB1* 0201 allele. In addition, patients carrying *HLA-DQB1* 0302 tended to have a higher risk of development of symptoms of BA [30]. According to J.C. Barrett et al. [81], the minor allele T of two SNPs (single nucleotide polymorphisms) in *HLA-DQB1* (rs9273349 and rs1063355) can apparently provide protection against both BA and T1DM. In addition, genetic analysis of TLR2 (toll-like receptor 2) showed that the T-allele in SNP rs3804100 is a predisposition allele for both BA and T1DM, and the C-allele is protective for both diseases [82].

M.F. Moffatt et al. [83] identified 9 regions with 10 SNPs associated with BA in a whole-genome study, among which the *ORLMD3/GSDMB* region was the only HLA antigen region common to both BA that began in childhood and T1DM [81, 83]. In the *ORLMD3/GSDMB* region, SNPs rs2305480 and rs3894194, associated with atopy, were also found to be associated with T1DM [83]. M.T. Heinonen et al. [84] in population-based association studies on T1DM and BA/allergic sensitization evaluated the role of *GIMAP4* and *GIMAP5* (GTPase of the immunity-associated protein) polymorphisms and found, that SNP *GIMAP5* (rs6965571) was directly associated with increased risk of both BA and allergic sensitization, but inversely associated with T1DM. SNP *GIMAP4* (rs13222905) was associated only with BA and allergic sensitization. At the same time, the study of Das Sudipta et al. [85] showed that chromosome 17q21 contains a cluster of genes, including *ORMDL3* and *GSDMB*, which are closely associated with both BA and type T1DM. An *ORMDL3* is located in the endoplasmic reticulum and regulates sphingolipids, metalloproteinases, remodeling genes and chemokines, as well as IL-6. An *GSDMB* is one of four members of the *GSDM* family (*GSDMA, GSDMB, GSDMC* and *GSDMD*) and responsible for the expression of TGF-β1, which is involved in the pathogenesis of BA. However, in the study, included 150 children with T1DM and 158 with BA, the authors found no differences in *IL-12R1* and *IL-12R2* gene polymorphisms in both groups of children with such diseases and in comparison to controls [1].

## CONCEPT "IMMUNE DYSREGULATION"

Studies conducted in the late XX and early XXI century showed that cytokines of both Th1- and Th2-immune response, which actively interact in the destruction of β-islet cells, are involved in the formation of T1DM. At the same time, the morphology of pancreatic lesions is different [86]. Meanwhile, Th1 pancreatic lesions in T1DM include focal limited insulitis consisting mainly of CD8+ and CD4+ T cells. And β-islet cells die by apoptosis, preserving the surrounding exocrine tissue. Th2 lesions consist mainly of eosinophils, macrophages and fibroblasts. And β-islets die as the result of necrosis. This results in the accumulation of fibroblasts, formation of extensive extracellular matrix and adipose tissue, which leads to tissue necrosis. In addition, macrophages infiltrating islets of Langerhans can secrete pro-inflammatory cytokines IL-1α, IL-1β, TNF-α, and various chemokines that promote the migration of dendritic cells, macrophages, and T lymphocytes [56, 80, 87]. It is often combined with increased levels of IL-2 in plasma [80] and its circulating receptor (CD25) in T1DM patients [56]. The kinetics of β-cell destruction also differ depending on the cytokines of the Th1/Th2-immune response: Th1 lesions are faster, more aggressive and persist for longer periods of time compared to Th2 lesions [22]. Consequently, Th2 lymphocytes and mediators are also actively involved in the pathogenesis of T1DM by facilitating infiltration by pancreatic mononuclear cells and accelerating the destruction of β-islet cells, which suggested, that T1DM is a Th1+ Th2-mediated disease [86, 88]. The progression of T1DM from insulitis (pancreatic mononuclear cell infiltration) to overt hyperglycemia is under the control of the Th1 and Th2 immune response and its respective cytokines [22].

Studies on animal models and people with T1DM confirm the direct role of Th1-lymphocytes and produced cytokines in the pathogenesis and progression of the disease, destruction of β-cells as a result of Th1-induced insulitis. IFN-γ and other cytokines act mainly at the level of activation of macrophages and CD8+ T-lymphocytes, increasing β-cell infiltration and thus accelerating its destruction through the release of preformed, *de novo* synthesized cytokines/chemokines and other mediators (nitric oxide, oxygen radicals, serinesterases…) [89]. In addition, cytokines of the Th1-immune response can induce activation and expansion of autoreactive T cells, as well as suppress the production of soluble cytokine an-

tagonists, including the IL-1 receptor antagonist. In turn, by enhancing β-cell destruction, it can lead to stimulation of IL-1 production by macrophages and significant increase in the expression of IL-2 and other Th1 cytokines [22]. At the same time, the predominance of Th1 cytokines in β-islet cell infiltrates in female but not male NOD mice (with genetically predetermined T1DM formation) has been described as a major predisposing factor for the development of anti-β-cell immunity and subsequent T1DM formation in females but not in males [22]. Consequently, the authors hypothesized that T1DM could be eliminated either by induction of the expression of cytokine of the Th2-immune response or by treating T1DM patients with drugs based on them (IL-4 and IL-10).

Recent studies more often show the possibility of common pathogenetic pathways in the formation of BA and T1DM, which may be based on *immune dysregulation* [9, 90]. For example, in evaluating the immunologic response in children with autoimmune/atopic diseases, it was shown that lipopolysaccharide (LPS)-stimulated peripheral blood mononuclears *in vitro* express a unique pattern of cytokines with a combination of both Th1 and Th2 immune response activity. Higher serum levels of IL-12 and IL-18 were found in children with a combination of BA and T1DM compared to controls. Moreover, IL-12 levels were lower in patients with both diseases compared to children with only one disease [91, 92]. The authors believe that this phenomenon is based on the depletion of mononuclear cells, which cannot increase IL-12 production. The IL-18/IL-12 ratio in serum *in vivo* was also significantly higher in children with a combination of BA and T1DM compared to patients with BA alone [91]. Meanwhile, IL-18 is a key pro-inflammatory cytokine produced by dendritic cells (DC), T- and B-lymphocytes, and macrophages. It is pleiotropic and interacts with a variety of cells. Its elevation is associated with exacerbation of BA [93]. IL-12 is also produced by DC, B cells and macrophages, but the main cellular targets are T lymphocytes and NK cells [87]. In the pathogenesis of T1DM, IL-12 and IL-18 can enhance the cytotoxic activity of T lymphocytes and NK cells, leading to impaired *immunoregulation* through alteration of T-reg cell activity [94].

## HYPOTHESIS ON THE ROLE OF T-REG CELLS

The hypothesis of T-reg cell overstimulation may be a promising hypothesis in studying the pathogenesis of T1DM+BA: patients with T1DM and allergy have higher levels of inflammatory cytokines compared to children with only one disease. At the same time, high cytokine levels persist despite hypersecretion of anti-inflammatory IL-10, suggesting functional depletion of T-reg cells [9, 95].

T-regs express P3 protein identified as a transcription factor essential for development and its function (forkhead box, FOXP3). Also T-regs are known to maintain immune homeostasis and prevent autoimmunity, playing an important role in formation of *immune tolerance to own tissues* [96], regulation of host-commensal microflora interactions, and tissue repair. The deficiency and/or dysfunction triggers autoimmune reactions and inflammation [97]. Immunosuppression mediated by T-reg cells can be provided by contact-dependent suppressor mechanisms, inhibitory receptors (CTLA-4, LAG3, galectin-1) or through perforin and granzyme, B-dependent cytotoxic killing of target cells [98]. In addition, T-reg cells can mediate contact-independent suppression by acting through IL-2 (T-reg cell-associated CD25) or by producing inhibitory cytokines such as IL-10, TGF-β, and IL-35 [99]. In addition to general suppressive activity, T-reg cells can additionally differentiate in the periphery and specifically control Th1-, Th2-, Th17-, or T follicular helper (Tfh) immune responses by acquiring the transcription program of the specific effector cells they suppress (T-bet, IRF4, STAT3, or Bcl-6, respectively) [100].

T-reg cells support a balanced adaptive immune response, protecting tissues both directly by repairing through the production of amphiregulin and indirectly by limiting tissue damage with suppressing the inflammatory response [97]. T-reg cells also protect against allergic diseases, transplant rejection, atherosclerosis, and control metabolic disorders [101]. Congenital genetic defects affecting the number and/or function of T-reg cells disrupt immune homeostasis, shifting the balance towards autoimmunity, lymphoproliferation, allergic dysregulation and ongoing lymphocytic infiltration of various organs, including the pancreas, resulting in disease progression. The spectrum of manifestations of T-reg cell defect may vary from mild allergic or autoimmune diseases to lethal outcomes of immune regulation. Thus, mutation of IL-2Rα/STAT5b and CTLA4/LRBA disrupts the homeostasis of the IL-2R-STAT5 signaling pathway and, consequently, the function of T-reg cells. The IL-2 receptor is known to consist of three subunits: α (CD25), β (CD122) and γ (CD132). CD25 binds IL-2 and is constitutively expressed in large numbers

by T-reg cells. Its deficiency impairs the suppressor function and metabolic activity of the latter due to its defective production of IL-10, as well as inability to bind and/or decreased sensitivity of CD25-deficient T-reg cells to IL-2 [102]. This leads to the development of both autoimmune disorders (alopecia, diabetes mellitus, thyroiditis, autoimmune hemolytic anemia, etc.): chronic eczema, enteropathy, lymphoproliferation, and immunodeficiency with recurrent infections caused mainly by herpes viruses [103–105].

It has also been found that children with the combination of BA and T1DM have increased spontaneous production of INF-γ, TNF-α and IL-10 by peripheral blood mononuclear cells (compared to the controls and patients with only one disease) [92]. Meanwhile, it is well known that IL-10 acts directly on Th2 cells. Its specific function is to prevent excessive inflammatory response, inhibit the activity of Th2-immune response and Th17-mediated reactions [106, 107]. The persistence of high levels of pro-inflammatory cytokines despite hypersecretion of anti-inflammatory group (IL-10) in patients with the combination of T1DM and BA [108] may indicate a deficit of regulatory mechanisms of the inflammatory response, its depletion and the inability of T-reg cells to additionally increase cytokine production [92]. This pattern characterized by *"depletion" of T-reg cells* may also be caused by a defect in TCD4+ inhibition, IL-10, HLA gene polymorphisms and CTLA-4 defects in combination with environmental triggers. *Consequently, a defect in IL-10 suppressive mechanism in patients with combined T1DM+BA may contribute to the development/progression of both atopic and autoimmune diseases* [109].

A number of authors have shown that in patients with combined T1DM+BA, T-reg and Th-17 can differentiate independently from Th1 and Th2 cells [110, 111]. At the same time, experimental studies using laboratory animals have established that in NOD model mice there may be an increase in Th2-mediated reactions and the development of experimental allergic asthma through the activation of CD1d-dependent NK cells. Its consequence is eosinophilia and the development of allergic inflammation. This suggests that autoimmune T1DM through activation of relevant cytokines may enhance the Th2-mediated immune response underlying the development of BA [112]. In mice with knockout of the gene encoding the IL-4 molecule, cytotoxic reactions mediated by Th1-lymphocytes may also be impaired. At the same time, knockout of *INF-γ* gene in NOD mice does not prevent T1DM [116, 113]. In addition, several studies have identified a special population of ILC (Helper innate lymphoid cells) that play a fundamental role in the early immune response. Thus, ILC2 participate in allergic reactions by activating the Th2 response, which contributes to an increase in the number of T-reg cells producing IL-10, and IL-C1, which initiates the synthesis of *INF-γ*. It seems to play a key role in the pathogenesis of inflammation in autoimmune diseases, including T1DM [9].

## EFFECT OF T1DM+BA ON DISEASE CONTROL

T. Hörtenhuber et al. [114] conducted a prospective multicenter observational cohort study, based on the DPV register (German-Austrian initiative — Diabetes-Patienten-Verlaufsdokumentation) and included 51 926 patients with T1DM under 20 years of age. The prevalence of BA in young patients with T1DM in Austria and Germany was studied, as well as its impact on metabolic control. Among all patients included in the study, 1755 (3.4%) had a combination of T1DM and BA. These patients were more often male (61% vs. 52%, p <0.01) and had a reduced height standard deviation (SDS) (–0.002±1.04 vs. 0.085±1.02, p <0.01) and increased body mass index (BMI)-SDS (0.31±0.89 vs. 0.28±0.89, p=0.04). The authors demonstrated that patients with combined T1DM+BA required higher doses of insulin to control T1DM (0.88±0.3 vs. 0.84±0.3 U/kg, p <0.01, respectively) and experienced more severe hypoglycemia (4.5 [4.2; 4.8] vs. 3.2 [3.2; 3.3] cases/100 persons per year, p <0.01). Glycosylated hemoglobin A1c (HbA1c) levels in patients with T1DM did not differ between patients with and without BA. However, differences were found depending on the therapy received by patients with BA (corticosteroids vs. leukotriene receptor antagonists, corticosteroids vs. sympathomimetics). Thus, those who was taking sympathomimetics had higher HbA1c value compared to the group taking other drugs. The authors suggested an anti-inflammatory effect of anti-asthmatic treatment, emphasizing the complex relationship between lung function, body mass index and glycemic control in children with T1DM. The high insulin requirement, they suggested, could be explained by additional stress, less physical activity and, therefore, slightly higher insulin resistance caused by inflammation, which may be related to both BA and/ or medications, primarily inhaled glucocorticosteroids (IGCS) and $\beta_2$-agonists. However, no effect of asthma

 ISSN 2221-2582

medications on metabolic control of T1DM or body mass index has been found [114]. According to J. Metsälä et al. [115], the use of some antiasthmatic drugs (IHCS, $\beta_2$-agonists) can be potentially associated with the risk of T1DM development, relative refractoriness of T1DM patients to BA due to its increased level of glucocorticosteroids with anti-inflammatory effect [34].

F. Ahmadizar et al. [116], used in their research Dutch PHARMO patient registration system, including children and adolescents under 19 years of age who received at least 2 insulin prescriptions between 1999 and 2009 (main group, n=915). The use of asthma medications and occurrence of BA exacerbations during 5 years before and after the onset of T1DM was studied. Control group consisted of 3590 patients of the same age and sex. The analysis showed that the 5-year prevalence of the use of medication for BA in patients with T1DM after its debut was significantly higher than in controls (23.2% vs. 18.3%, respectively). There was no statistically significant difference between groups in the use of specific medications for treatment of BA, with the exception of short-acting M-cholinolytics, which were significantly more frequently used in the group of children with combined T1DM+BA compared with controls (5.5% and 0.62%, respectively). Consequently, the authors believe that T1DM is associated with a statistically significant higher use of antiasthmatic medications after the onset of type 1 diabetes mellitus, especially in the first year after the onset of the disease [116]. Children with T1DM and treated for BA had significantly fewer episodes of hypoglycemia and better glycemic control compared with children with only T1DM. Perhaps, the authors believe, the drugs used for treatment of BA, particularly $\beta_2$-agonists, have therapeutic potential to reduce hypoglycemia and contribute to improved glycemic control [116]. The authors collected data on 226 children, of whom 27 (12%) were being treated for BA. Only 11 (out of 27) children were taking their prescribed inhaled glucocorticosteroids. But all children were taking $\beta_2$-agonists at least once a week. At the same time, the frequency of hypoglycemia in children with T1DM and treated for BA decreased by 20%. In children with T1DM and treated for BA, 52% reported an episode of hypoglycemia in the previous three months, compared with 72% of children who had T1DM only. There were no differences in the proportion of children with nocturnal or severe hypoglycemia. Although not significant, but children with the combination of BA+T1DM had better overall control compared to children with T1DM alone (HbA1c 8.8%, HbA1c 9.3%, respectively). T.D. Wu et al. [117], M.H. Black et al. [44] also found a correlation between T1DM and BA and demonstrated a higher rate of BA in children and adolescents with T1DM. Scientists also demonstrated an association between concomitant BA, poor glycemic control in patients with T1DM (HbA1c: asthma + T1DM: 7.77±0.26% (61.4±2.0 mmol/mol) vs T1DM alone: 7.49±0.2% (58.4±1.5 mmol/mol), p=0.034), HbA1c levels and exacerbation of BA in patients, especially if BA was untreated, i.e. patient did not receive baseline therapy [44]. Similar data on the higher prevalence of BA in children with T1DM and poor glycemic control affecting the course of BA were shown in the study of Hsiao et al. [43] and H. Villa-Nova et al. [46]. In the work of G. Yang et al. [78] it was also reported about the negative association between HbA1c and exacerbation of BA in 47,606 adult patients in the UK. It was also found that perhaps these two diseases can influence the rate of achieving control of each other.

## CONCLUSION

Thus, modern epidemiological studies show that the relationship between type 1 diabetes mellitus and bronchial asthma is much deeper and more complex than the existing Th1/Th2 paradigm. Allergic and autoimmune diseases are comorbid pathologies, which are closely interrelated, and affect the onset, sequence of clinical symptoms, pattern of control, and characteristics of each other's therapy. Scientific data indicate the existence of a common complex polygenic basis for the formation of T1Dm and BA. At the same time, it is possible that the genetic differences discovered in the study of patients with a combination of BA + T1DM may be of decisive importance in the relationship between type 1 diabetes mellitus and bronchial asthma.

However, research in this direction should also be continued. The current understanding of potential pathogenetic and immunological triggers that play a decisive role in the onset, course and therapy of BA+T1DM combination can be represented as a triple relationship between *genetic environmental factors and unique cytokine profile in these patients.* The multifactorial relationship should currently be considered as bidirectional in nature, given that each element of this system affects others without a clear sequential order of occurrence. At the same time, pathogenesis

of combined pathology (T1DM+BA) is based on *immune dysregulation with cytokine imbalance (decrease in number and depletion of the reserve capacity of T-reg cells, as well as defect in the suppressive mechanism of IL-10)*. The consequence of this is appearance/intensification of inflammatory process, imbalance of autoimmunity mechanisms, which is accompanied by an even greater disruption of immune homeostasis and formation/progression of symptoms of both BA and T1DM.

That is why physicians should be aware of possible coexistence of autoimmune and atopic/allergic diseases (BA+T1DM), complex mutual influence on each other's onset, common pathogenetic mechanisms of temporal connection, influence on the course and pattern of disease control, as well as the specifics of therapy. It is needed to improve management of patients, increase their quality of life and form a favorable prognosis.

## ADDITIONAL INFORMATION

**Author contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

**Competing interests.** The authors declare that they have no competing interests.

**Funding source.** This study was not supported by any external sources of funding.

## ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

**Вклад авторов.** Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

**Источник финансирования.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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