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Allergies and Obesity in Children: Is There a Connection?

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Abstract: The steady increase in the prevalence of chronic non-communicable diseases in the population, including obesity and allergic diseases, dictates the need for both the study of common causal factors and the mechanisms of their development, and the search for new effective treatment and preventive strategies. However, the results of epidemiological, clinical and laboratory studies are still inconclusive, especially in the pediatric population. This review presents and discusses current data that provide an opportunity to understand the possible relationship and mechanisms of interaction between allergies and obesity in children.

Key words: allergy, obesity, bronchial asthma, allergic rhinitis, atopic dermatitis.

At present, the problem of obesity and overweight, which is detected in every fourth inhabitant of our planet, has become relevant in all age categories and has acquired a global character [1]. In addition to the growing prevalence, which has already been classified by many scientists as an epidemic, a group of diseases associated with obesity is of great concern to specialists: arterial hypertension, non-alcoholic fatty liver disease (NAFLD), Studies show that these conditions can be a consequence of obesity, and their occurrence is associated with a direct change in the immune system in conditions of excess body weight, primarily with the formation of chronic non-infectious inflammation [2]. In addition, in recent years, there have been many indications of a link between childhood obesity and allergic diseases, due to common epidemiological trends, risk factors, pathogenetic mechanisms and potential for treatment and prevention. The purpose of this review is to systematize the data accumulated to date on the relationship and interaction between allergies and obesity in children EPIDEMIOLOGICAL TRENDS

The epidemic pattern of the increase in the prevalence of allergic diseases and obesity in all age groups, including the child population, recorded over the past decades in most countries of the world, suggests the existence of an underlying relationship between these conditions. The results of the large-scale International Study of Asthma and Allergy in Children (ISAAC), which analyzed the data of more than 1,200,000 patients, indicated a clear trend towards an increase in the prevalence of various manifestations of allergies both in developed countries and in countries with a low socioeconomic level [3]. At the same time, the prevalence of asthma, allergic rhinoconjunctivitis and eczema in children aged 13–14 years was 14.1%, 14.6% and 7.3%, and in children aged 6–14 years.

7 years — 11.7%, 8.5% and 7.9%, respectively. The prevalence of obesity is also progressively increasing, which 40 years ago was diagnosed in no more than 1% of all children in the world (5 million girls and 6 million boys). However, in 2016, 5.6% of girls (50 million) and 7.8% of boys (74 million) suffered from it. The number of overweight children and adolescents increased by 213 million in 2016 compared to 1975 [4]. Epidemiological studies show that in all regions of the world, the number of obese and overweight children is steadily increasing and doubling every three decades [1].

At the beginning of the new millennium, many researchers began to note a positive association between the presence of obesity and clinical manifestations of allergies or the level of total IgE in the blood serum as a marker of atopy [5, 6], as well as to consider obesity as a risk factor for asthma and a predictor of its severity [7]. One of the first such studies conducted in the United States revealed a positive correlation between levelsTotal IgE in children aged 2 to 19 years not only with body mass index (BMI), but also

with Reactive Protein [8]. However, the results of other studies were not so unambiguous [9–11], which could be due to differences in the design of the studies, the age of the population studied, socioeconomic characteristics, as well as the methodological and diagnostic approaches used [12]. The revealed contradictions spurred scientific interest in the problem of the relationship between allergies and obesity and led to a significant increase in the number of basic and clinical studies in this area. Their results deserve attention not only due to the commonality of epidemiological trends (obesity and allergic rhinitis, asthma, atopic dermatitis), including in certain age groups, but also due to the similarity of hypotheses considering the immunobiological and epigenetic mechanisms of the development of these conditions.

COMMONALITY OF PATHOGENETIC MECHANISMS

Currently, there are many hypotheses explaining the possible relationship between obesity and atopy. The most important of them is based on data on changes in the functioning of the human immune system in overweight conditions, associated mainly with an increase in the production of inflammatory mediators and the formation of chronic non-infectious inflammation [8].

Obesity is a chronic disease associated with systemic inflammation characterized by the presence of CD4 and CD8 T-cell infiltration and modification of the immune response, which in turn contributes to the development of obesity-associated metabolic and immunopathological conditions [13]. In particular, the role of peripheral Treg and Th17 lymphocytes, which show a pronounced imbalance in overweight patients with metabolic dysfunction, has been well studied. However, to a greater extent, obesity is considered as a chronic non-infectious inflammation characterized by changes in the natural levels of adipokines and cytokines [14]. Leptin and adiponectin are the main peptide hormones of adipose tissue (adipokines) involved in the metabolism of glucose and lipids, regulating energy metabolism, but at the same time playing the role of cytokines [15]. Leptin, due to its physiological endocrine features, has an anorexigenic effect (suppresses appetite, stimulates the sympathetic nervous system), and as a cytokine it has pro-inflammatory properties, i.e. it contributes to the development of inflammatory reactions [16]. For example, leptin is involved in the reactions of apoptosis, proliferation and activation of T-lymphocytes, while the general effect of leptin on memory T-cells is to enhance T-H1 responses and suppress T-H2 and regulatory T-cell responses. It has been shown that increased levels of circulating leptin in blood serum in obese patients correlate with non-specific inflammation, as a result of which the risk of developing diseases associated with excess weight increases. In addition, leptin is a mitogenic keratinocyte factor that supports fibroblast proliferation, and its level is positively correlated with the percentage of body fat: the higher the degree of obesity, the higher the level of leptin in the blood serum [17]. The data presented in the literature indicate that the level of leptin in the blood serum increases during allergic reactions from the respiratory tract and correlates with their severity [16].

On the other hand, obesity has a decrease in the plasma level of another adipokine, adiponectin, which is an endogenous anti-inflammatory bioactive polypeptide secreted by fat cells and involved in the regulation of non-infectious inflammation in obesity [17]. Thus, leptin and adiponectin have opposite effects on the immune response and are in a state of reciprocal interaction: the higher the level of pro-inflammatory leptin, the lower the level of adiponectin, which has anti-inflammatory properties, and vice versa. Another protein that has attracted attention regarding the link between obesity and allergies is osteopontin, a pro-inflammatory cytokine that can be secreted by many osteoblast cells, fibroblasts, epithelial cells, as well as activated macrophages and T-lymphocytes [18]. It is found in various tissues (bone tissue, kidneys, muscles, bladder) and is found in biological fluids. Osteopontin is an integral part of the extracellular matrix of the central nervous system, and its production in tissues increases in response to inflammation or injury [19]. It has been shown that the level of osteopontin correlates with the number of eosinophils in the human peripheral blood and increases after activation by granulocyte-macrophage colony-stimulating factor and IL-5. Moreover, recombinant osteopontin promotes eosinophil chemotaxis in *in vitro* experiments [20]. In addition, several recent Korean studies in children with allergic rhinitis and obesity have shown a statistically significant increase in serum levels of osteopontin and leptin compared to controls (healthy children), their positive correlation with the number of blood eosinophils and the severity of the disease [18,

21]. that increased levels of leptin and osteopontin in allergic rhinitis slow down apoptosis, adhesion, migration and activation of eosinophilia, leading to the development of eosinophilia, one of the main pathogenetic mechanisms of allergic inflammation.

It is important to note that the pathogenetic mechanisms underlying the possible relationship between allergies and obesity are not yet fully understood, but the immune nature of this association is obvious, and evidence of which is also available in pediatric patients. For example, system-wide changes in immune function in obesity described for reactions to infection (including the determining more severe course of COVID-19), vaccination, and malignant neoplasms are indisputable [22]. Recent studies in the Netherlands have demonstrated an excessive number of some subpopulations of lymphocytes (Vδ2 +Vγ9+ and CD8 +TEMRO) in children with a higher visceral fat index, which may indicate the presence of chronic inflammation, as well as in obese adults [23]. Moreover, a systematic analysis of 26 reviews examining the relationship between childhood obesity (or their

During pregnancy) and the functioning of the child's immune system confirmed the association between childhood obesity and significant shifts in serum levels of anti-inflammatory cytokines and proteins, as well as the number and activity of immunocompetent cells [24]. At the same time, maternal obesity increases the risk of developing bronchial asthma in the unborn child. The identified changes, according to the authors, can not only cause exacerbations of many diseases, such as asthma, allergies, atopic dermatitis and obstructive sleep apnea syndrome, but also reduce the child's immune response to vaccines and pathogens. Thus, despite the large amount of evidence of the impact of childhood obesity on the development and functioning of the child's immune system, the possibility of developing allergic diseases and the severity of their course, there is currently a need for further research in this area to clarify the mechanisms of the relationship between excess body weight in children and specific immunopathological conditions.

HYPOTHESES OF GENERAL EPIGENETIC PROGRAMMING

The growing interest in the connection between diseases that have been characterized by epidemic spread in recent years (including allergies and obesity) has led to serious reasons for searching for their relationships at the level of epigenetic programming.

First of all, this applies to nutrition as the most important determinant of a child's immune health [25]. Today, no one doubts that a person's diet not only has a serious impact on his health in general, but also determines the risk of developing obesity and many associated diseases. For example, the consumption of a high-calorie diet against the background of frequent overeating and a sedentary lifestyle (the so-called Western life style) leads to the development of chronic metabolic inflammation, which has been scientifically defined as metainflammation [26]. This non-infectious minimal persistent inflammation, associated with changes in the functioning of immune system cells under the influence of modern lifestyles and Western diets, underlies the development of not only metabolic disorders, but also other chronic non-communicable diseases, which include allergies, asthma, autoimmune diseases and cancers, which is a growing public health problem with global epidemic proportions.

However, in recent years, more and more attention has been paid to the influence of nutrition on the development of a child at an early age and even in the antenatal period. There is emerging evidence that exposure to various factors during pregnancy, infancy and early childhood, among which nutrition plays a key role, can modify gene expression and change the susceptibility of the child to the subsequent development of various diseases, in particular obesity, asthma and allergies [27]. At the same time, modern dietary features (for example, a reduced content of vegetables, beans and fish) lead to a decrease in the anti-inflammatory activity of many nutrients - prebiotics, oligosaccharides, antioxidants, omega-3 polyunsaturated fatty acids, folate and other vitamins that normally modulate the programming of metabolic and immune regulation. As a result of this epigenetic programming, there is an increased risk of chronic inflammation and immune disorders seen in patients with obesity, asthma and allergies.

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Vitamin D deficiency is considered as another possible epigenetic factor that combines obesity and allergic diseases.

Currently, the role of vitamin D in the regulation of innate and adaptive immunity and its influence on the mechanisms of epigenetic programming that determines the risk of developing allergic and autoimmune diseases, as well as reducing the response to viral and bacterial pathogens, is well studied [28]. Numerous studies to date confirm the existence of a positive association between a decrease in sun exposure and circulating 25-hydroxyvitamin D with allergic diseases and bronchial asthma, especially in the pediatric population [28–30]. At the same time, a systematic review and meta-analysis of 23 studies on the relationship between obesity and vitamin D deficiency confirmed the existence of a direct association between these conditions, regardless of age, geographical location, and the difference in vitamin D thresholds used in the study [31]. Moreover, there is evidence of a link between D deficiency in childhood obesity and a high level of circulating inflammatory mediators [32], as well as with the severity of bronchial asthma [33]. Thus, there is increasing evidence that hypovitaminosis D can lead to impaired immune and metabolic programming of the fetus and young child, which is one of the possible explanations for the alleged link between obesity and allergic diseases in children [34].

When discussing the hypotheses of the epigenetic relationship between obesity and allergies, it is impossible to avoid the question of the role of the microbiome in the regulation of intestinal and systemic immunity and the mechanisms of its influence on the development of the child's immune system and his metabolic phenotype [35]. The results of current studies demonstrate changes in the metabolome of the liver, serum, urine and adipose tissue in obesity, as well as a significant disruption in the composition of the intestinal microbiota. This may be important for patients with asthma in the setting of obesity, as it is accompanied by excessive production of certain metabolites (short-chain fatty acids and bile acids) that have an effect on pulmonary functions and contribute to the maintenance of systemic inflammation through changes in host metabolism, insulin sensitivity, eating behavior, and the effect on IL17A immune cells. In addition, the lung microbiome also changes in overweight conditions, which has a negative impact on the course of asthma and the response to medication [36].

The assumption that changes in the intestinal and/or pulmonary microbiome occurring in obesity contribute to the course of allergic diseases, in particular asthma, has several important therapeutic applications. On the one hand, it is likely that the development of a child's immune system can be influenced by factors that affect the intestinal microbial communities, including environmental interventions or contact with external bacteria. On the other hand, the use of probiotics (and in some cases fecal transplantation) seems to be a promising strategy for the treatment of many obesity-associated diseases and is already used in clinical practice in some nosological forms [37]. At the same time, it has been shown that a high-fiber diet in obese children is accompanied not only by the suppression of laboratory signs of inflammation, but also by the weakening of virulence genes in intestinal microbes [38]. Thus, a better understanding of the role of the gut and pulmonary microbiota in the development and maintenance of obesity and its associated metabolic and immunopathological processes may provide new avenues for the treatment of therapeutically complex patients with co-occurring diseases.

OBESITY AND ALLERGIC RHINITIS

Allergic rhinitis (AR) is one of the most typical representatives of atopic diseases and is characterized by chronic eosinophilic inflammation and an IgE-associated response to allergens [39]. Despite the fact that AR and obesity/overweight have common comorbid conditions and belong to conditions characterized by the presence of chronic inflammation, the pathogenetic mechanisms of their relationship are currently not fully understood, are associated mainly with changes in the production of pro-inflammatory and anti-inflammatory adipokines and cytokines, and are presented in more detail earlier [15–18, 21].

At the same time, the results of large-scale epidemiological studies indicate a positive correlation of obesity with allergic rhinitis and chronic rhinosinusitis in both adult and pediatric populations [40]. Interestingly,

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according to data presented in 2016 by the Centers for Disease Control and Prevention in the United States, obesity in adults was more often associated with an increased likelihood of developing non-allergic rhinitis. while in children, a higher body mass index (BMI) correlated with the presence of allergic rhinitis and atopy [41]. Similar results were obtained in a large-scaleChinese study conducted as part of the National Study of Allergy and Asthma in Children and included the analysis of a questionnaire of more than 3 thousand respondents [42]. Given some contradictions in the published materials, in 2020, a group of Chinese scientists conducted the first meta-analysis of 30 studies (the total number of participants is more than 261000) that studied the association of BMI and the presence of AR in adults and children [43]. Despite heterogeneity of the studies included in the analysis, the authors were able to show that obesity/overweight was associated with a higher risk of AR in the pediatric population, but not in adults. A possible reason for the identified association is the immune-mediated inflammatory process underlying both pathological conditions, which in children is combined with the impact of additional factors, in particular, a decrease in physical activity against the background of comorbid conditions (asthma, atopic dermatitis), leading to weight gain, or side effects of medications.

Of course, subsequent studies should be aimed at a deeper study of the role of obesity/overweight in the development of AR, as well as the mechanisms of their mutual influence in order to use the information obtained in order to plan targeted therapeutic and preventive interventions.

OBESITY AND BRONCHIAL ASTHMA

A large group of conditions associated with obesity is occupied by diseases of the bronchopulmonary system (hypoventilation syndrome, pulmonary hypertension, the course of chronic obstructive pulmonary disease against the background of obesity, obstructive sleep apnea, bronchial asthma (AD) associated with obesity), due to the peculiarities of its functioning in conditions of excess body weight. Many of them significantly worsen the quality of life and lead to early disability, especially in childhood.

A large number of epidemiological studies indicate an association between the presence of obesity and asthma, especially in the pediatric population and in females [44–46]. Combining their findings, it can be argued that a higher incidence of asthma is found in obese/overweight adults and children, who also have a more severe asthma course and a poor prognosis. In addition, there is evidence that the course of AD worsens when gaining weight in people who were previously of normal weight, and in some obese patients, the response to AD therapy is worse than in people with a normal body mass index [47].

One of the main reasons that affects lung function in overweight people is the type of distribution of subcutaneous fat (FAA) [48]. As you know, obesity can be of two types: central (abdominal) and peripheral (gynoid). The abdominal type of obesity is characterized by the predominant deposition of PFAs in the anterior abdominal wall and plays a decisive role in the formation of insulin resistance, hypoxia, and the occurrence of non-infectious inflammation. As a result, such patients have a significantly higher risk of developing cardiovascular pathology and a more severe course of metabolic disorders and other diseases associated with obesity [49]. In addition, the abdominal type of obesity plays a significant role in the occurrence of bronchopulmonary pathology due to changes in the mechanical function of the lungs due to the deposition of PFAs in the mediastinum and diaphragm, which leads to an increase in intra-abdominal and pleural pressure, a decrease in the functional residual capacity of the lungs, and an increase in the average respiratory rate [50]. A study of lung function in children with AD and obesity demonstrated that overweight and obesity were associated with signs of peripheral airway obstruction [51].

It is obvious that the mechanical factor may be one of the important conditions contributing to the development of bronchopulmonary pathology in obesity and having a negative effect on the course of AD in overweight patients. However, the relationship between these pathological conditions is based on chronic non-infectious inflammation resulting from immune dysfunction and accompanied by dysregulation in the leptin-adiponectin system [15–18, 21]. In the case of AD, as well as in AR, there

is an excess production of leptin, which has a significant impact on the functioning and development of the bronchopulmonary system in the intrauterine and neonatal periods, and is involved in the production of surfactant and lung development in newborns [52]. In addition, increased leptin secretion suppresses immune T cell function and can stimulate leukotriene production, increase IgE secretion, and increase the production of inflammatory mediators, leading to an inflammatory response not only from the upper respiratory tract but also from the bronchi. In turn, a decrease in adiponectin, which has effects opposite to those of leptin, may also be a risk factor for the development of AD in children [53]. Another important aspect characteristic of the AD phenotype in obese children is the predominance of neutrophilic inflammation over eosinophilic inflammation [54]. In the sputum of such patients, not only a large number of neutrophils is detected, but also a high level of IL-17, which is associated with neutrophilic inflammation and can cause resistance to glucocorticosteroid therapy, as well as increase the severity of AD [55]. At the same time, IL-17 is also associated with obesity as one of the cytokines involved in non-infectious inflammation [56]. In addition, monocytes in obesity produce monocytic chemoattractant protein 1 and tumor necrosis factor alpha, which indirectly lead to neutrophilic bronchial infiltration and the development of AD [48].

Thus, the pathophysiological mechanisms underlying the relationship between AD and obesity can be divided into three main categories: changes in the mechanical function of the bronchopulmonary system, nonspecific inflammation in obesity, which is one of the triggers for the development of AD and aggravates its course, and the predominance of the neutrophil component, which requires a separate approach to therapy. However, the exact causes of asthma in obese children are still unclear, which requires further study of the relationship between these diseases.

OBESITY AND ATOPIC DERMATITIS

The complexity of pathophysiological mechanisms and the wide range of clinical phenotypes are the cause of serious diagnostic and therapeutic problems in the management of patients with atopic dermatitis (AD). Obesity is considered one of the important risk factors for the development and severe course of the disease [57, 58], on the contrary, children with severe AD are more likely to show signs of metabolic syndrome [59]. There is evidence of higher levels of total cholesterol in patients with AD (especially those with severe disease) compared to healthy people [60]. Interesting results were obtained in a study that studied the level of leptin in primary school children with AD: an inverse correlation was found between the severity of AD (SCORAD index) and the level of serum leptin, while its concentration was statistically significantly higher in patients with non-atopic AD, as well as in the case of its mild course [61].

Since dry skin is the most important component of the development and severe course of AD, it is important to pay attention to the contradictory results of studies that examined the relationship between obesity (BMI) and transepidermal moisture loss (TEW) [62, 63]. Despite some contradictions in the published materials, a systematic review and meta-analysis of observational studies that examined the possible association between obesity and AD confirmed the existence of such a relationship, with the strongest correlation being found in childhood [64]. However, the authors draw attention to the need for larger cohort studies to clarify the association, as weight loss measures in patients with AD and obesity may be effective in maintaining control of AD symptoms.

CONCLUSION

In this review, we have summarised the evidence to date on the epidemiological, immunobiological and epigenetic relationship between obesity/overweight and allergic diseases in children. In our opinion, an interesting fact is that the prevalence of allergic rhinitis/chronic rhinosinusitis and atopic dermatitis is higher in the groups of obese patients than in patients with asthma and food allergies, which may be partly due to the participation in the pathogenetic mechanisms of these nosological forms of IL-17 [40]. In addition, in experimental models, mice knocked out at receptor A IL-17 (IL-17RA) fail to induce the development of obesity, and allergic diseases with a high degree of

involvement of type 3 of inflammation (IL-17-dependent response) have a more pronounced correlation with obesity [65], which may be important for choosing the right therapeutic strategy. The data presented in the review require a deep understanding of the mechanisms underlying the comorbidity of patients with various pathological conditions, in particular allergies and obesity, provide an opportunity to reassess the problems of ineffectiveness of their therapy and open up new prospects for creating approaches to prevention and treatment.

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