



# **Disorders of the Immune System and Susceptibility to Various Diseases in Children with Diabetes Mellitus**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

The article examines the features of emerging disorders of the immune system in children suffering from diabetes mellitus, as well as the susceptibility of such children to various diseases. The authors note that children with diabetes have some disorders of the immune system, which, combined with high glycemia, increase the risk of infections and their severity, and they should be immediately detected and treated.

Infections, even typical childhood diseases, significantly interfere with glycemic control. As a result of the infectious process, the level of counter-regulating hormones, cortisol, adrenaline and growth hormone increases, which leads to increased neoglycogenesis, glycogenesis and increased insulin resistance. This increase in insulin resistance requires adjustment of the patient's usual insulin dose, both basal and bolus. There are usually several hours or days before such a need arises, and it may take time to increase the dose, which can lead to hyperglycemia during this period. The presence of an infectious condition, in turn, increases blood glucose levels and increases the risk of decompensation, so pediatricians should be warned against the need to strengthen monitoring and insulin therapy. Patients with diabetes are often not fully vaccinated against various diseases. Vaccines are vital for these patients, significantly reducing the risk of infections and exacerbating the development of the underlying ailment.

**Keywords:** Immune system; childhood; diabetes mellitus; diseases.

## 1. INTRODUCTION

At the present stage, the incidence of diabetes among children and adolescents around the world is quite common. The development of diabetes mellitus negatively affects the overall health of the child, reducing the immune response of the body, which acts as the primary basis for the predisposition of the child's body to the incidence of both infectious and non-communicable diseases [1]. For this reason, issues related to the peculiarities of the management of children's patients suffering from diabetes mellitus of various types are highly relevant to consider, since to prevent the growth of such diseases, it is necessary to understand the nature and mechanism of their occurrence.

The work aims to analyze possible factors and ways of developing diseases of various genesis in children suffering from diabetes mellitus, as well as to determine methods to minimize the dangerous consequences of the development of such diseases for children's health.

## 2. MATERIALS AND METHODS

In the process of writing this work, various aspects of the morbidity of children diagnosed with type 1 and type 2 diabetes mellitus were investigated, taking into account the decrease in their immune response, highlighted in the special literature. Analytical and comparative methods were used in the study of the selected information array.

## 3. RESULTS

Children suffering from diabetes, unlike their healthy peers, are significantly at risk of developing various additional diseases. For example, hypertension is a known risk factor for

diabetes-related comorbidities, such as nephropathy. An increase in systolic blood pressure increases the likelihood of developing diabetic nephropathy, which underscores the importance of correcting hypertension in diabetics.

The authors study multiple mechanisms of increasing blood pressure in patients with diabetes. In particular, in some studies, there is an opinion that there is a direct connection between the gut microbiome and blood pressure.

Based on the presented data, conclusions follow that the composition of the intestinal microbiota in children with diabetes differs significantly from their peers who do not suffer from diabetes. Such differences can lead to changes in the inflammatory environment and the production of short-chain fatty acids. Both of these factors affect pancreatic function in patients [2].

Patients with diabetes mellitus may show several changes in their microbiome: changes in the skin flora, including increased colonization by *Staphylococcus aureus*, skin lesions favoring chronic hyperglycemia, and changes in the gut microbiome caused by disease or treatment.

A high diversity of the intestinal microbiota usually indicates a healthy microbiome, which can be assessed by measuring alpha diversity (*Observed* and *Chao1* indices for measuring species richness and *Shannon* and *Simpson* indices for species abundance) and beta diversity (*Bray-Curtis* dissimilarity index) [3].

The exact balance of the gut microbiota is crucial, and any disruption of its balance can affect health due to the complexity and relationship with pathogenic bacteria.

One of the potential mechanisms by which the gut microbiota can contribute to the pathogenesis of high blood pressure is the activation of an inflammatory response through microbial intestinal dysbiosis, which can eventually lead to endothelial dysfunction caused by nitric oxide (NO), as shown in hypertension associated with diabetes. NO is an unstable free radical that plays an important role in the regulation of blood flow, relaxation of smooth muscles, immunological responses, differentiation and cell death. Under normal conditions, it lowers blood pressure due to its vasodilating activity, and the intestinal microbiota is reported to regulate its production.

During activation, inflammatory response NO is produced by the inducible enzyme NO-synthase and is released in abnormally high amounts from immune cells. This NO combines with superoxide radicals ( $O_2^-$ ) to form peroxynitrite ion ( $ONOO^-$ ), causing toxic effects on blood vessels, increasing oxidative stress, protein nitration and increasing cellular proliferation. All these effects cause damage to the endothelium, which leads to an increase in the release of vasoconstrictors and, ultimately, to hypertension [4].

The relationship between diabetes mellitus and infections is of great interest and is the reason for significant discussions in the medical literature. Several studies have evaluated this association, mostly in adults, but many have also evaluated the impact and frequency of infections in children and adolescents with diabetes mellitus. It is believed that, in addition to the usual community-acquired infections, some infections occur mainly in patients with diabetes, and other common infections may be more aggressive in these patients. It was also noted that adequate glycemic control improves immune function and reduces morbidity and mortality associated with severe infections in patients with DM.

It is important to remember that diabetes mellitus is classified according to the etiopathogenesis of the disease, the most common of which is type 2, especially in adults, followed by type 1, especially in children and adolescents [5].

Type 1 diabetes mellitus is caused by an autoimmune process directed against the beta cells of the pancreas responsible for the production and secretion of insulin, which leads to their destruction, followed by insulin deficiency and hyperglycemia.

Type 2 diabetes mellitus is caused by metabolic changes, including the presence of peripheral insulin resistance associated with secondary.

Pancreatic insufficiency is the most common type in adults, which is closely associated with obesity and insufficient physical activity. Although most children and adolescents suffer from type 1 diabetes mellitus, there has been an increase in the incidence of type 2 diabetes mellitus for several years due to an increase in the prevalence of overweight and obesity in this age group.

It is noted in the literature that children suffering from diabetes mellitus may be exposed to various infections. Thus, respiratory infections are the main cause of infection in children, including those with diabetes.

The main etiological agents of lower respiratory tract infections are *Streptococcus pneumoniae* and respiratory viruses, including influenza viruses [6].

Although the prevalence of pneumococcus in children with diabetes does not increase in healthy children or patients with other chronic diseases, some studies have shown that patients with diabetes have the highest susceptibility of the body to pneumococcal infection and higher mortality in the presence of this infection.

It is also quite common for children suffering from diabetes to develop candidiasis. The most frequent localization is the vulvovaginal region, and the risk is higher depending on the type of diabetes, severity and degree of glycemic control. Patients with type 1 diabetes with elevated levels of glycated hemoglobin and inadequate glycemic control are more likely to have *Candida spp* colonization.

Hyperglycemia worsens neutrophilic functions, including phagocytosis, acting as a nutrient for *Candida*, resulting in increased adhesion of the fungus to epithelial cells.

The clinical diagnosis in patients with vulvovaginitis candidiasis is based on typical clinical signs, such as thick whitish vaginal discharge, itching, pain, burning, erythema and edema. Patients with diabetes may have recurrent diseases with a frequency of up to four episodes per year [7].

Also, in children and adolescents with type 1 diabetes mellitus, especially in poorly controlled patients, the frequency of periodontal infection is two to three times higher. A predisposing factor is a change in gum vascularization in addition to immune deficiency. Periodontitis can lead to loss of ligaments, mobility of teeth and the need for removal. Dental abscesses and bacteremia are possible.

Urinary tract infections are more common in children suffering from diabetes, and they may also have severe complications and manifestations.

Some factors contribute to a higher risk of urinary tract infections: weakened immunity, incomplete emptying of the bladder due to autonomic neuropathy and impaired metabolic control, since elevated glucose levels in urine also contribute to colonization by pathogenic microorganisms. The most common pathogens are the same as in the general population: *Escherichia coli* and other Enterobacteria.

The most common infections are asymptomatic bacteriuria, urinary tract infections of the lower parts (cystitis), upper urinary tract (pyelonephritis) and urosepsis. Complications such as renal papillary necrosis and a renal abscess may also occur.

Infections of the skin and soft tissues are also often diagnosed in children with diabetes, especially with insufficient glycemic control. Candidiasis, bacterial infections, dermatomycosis and onychomycosis are possible.

Also, children suffering from diabetes mellitus may be diagnosed with necrotic fasciitis. Necrotic fasciitis is a rare and severe infection with a high mortality rate (50-70%). Diabetes mellitus is a predisposing condition most often associated with this infection, which affects subcutaneous cell tissue and muscle fascia, causing extensive necrosis.

Suspected clinical signs: skin lesions, no response to initial antibiotic therapy, hardened subcutaneous tissue extending beyond the affected area of the skin, toxicosis, bullous lesions, skin with areas of necrosis and bruising, as well as the presence of crepitation. The clinical picture includes toxicosis, fever, lethargy, cellulite (90% of cases), edema (80%), skin discoloration or gangrene (70%) and anesthesia of the affected area of the skin [8].

Computed tomography or magnetic resonance imaging can show edema extending beyond the fascial plane. The most affected areas are the extremities, abdominal wall and perineum.

Surgical intervention is the main treatment with the maintenance of antibacterial therapy until surgical procedures are no longer necessary, the patient will have clinical improvement and will not have fever for more than 48 hours.

Also, some researchers have noted that children suffering from diabetes may have a history of malignant otitis externa. This is an invasive infection of the external auditory canal and the base of the skull that occurs in elderly people with diabetes. More than 98% of cases are caused by *Pseudomonas aeruginosa*. In rare cases, it can be caused by *Aspergillus* or other fungi. The predisposing factor is microangiopathy of the auditory canal.

The clinical picture includes severe headache, otalgia, otorrhea, and deafness, which can last from months to years. In this place, cellulite can develop together with focal neurological signs, paralysis of cranial nerves and osteomyelitis of the bones of the base of the skull and the temporomandibular joint. Otoscopy shows granular tissue in the auditory canal without damage to the eardrum. Treatment should be systemic with the use of antibiotics against *Pseudomonas*, the most commonly used quinolones, for six to eight weeks; and surgical treatment of the wound, if necessary.

#### 4. DISCUSSION

Achieving optimal glycemic control in children and adolescents with diabetes is crucial and can prevent an increased risk of infection. However, in this age group it is very difficult to achieve adequate metabolic control, which is currently considered to be the level of glycated hemoglobin below 7.0 % [9].

It is indisputable that infections, even typical childhood diseases, significantly interfere with glycemic control. As a result of the infectious process, the level of counter-regulating hormones, cortisol, adrenaline and growth hormone increases, which leads to increased glycogenesis and increased insulin resistance.

This increase in insulin resistance requires adjustment of the patient's usual insulin dose,

both basal and bolus. There are usually several hours or days before such a need arises, and it may take time to increase the dose, which can lead to hyperglycemia during this period.

Persistent hyperglycemia can lead to an increase in the production of ketone bodies. The development of this condition can lead to diabetic ketoacidosis, which is the main cause of death in young patients with type 1 diabetes mellitus.

To avoid deterioration of metabolism and minimize the risk of diabetic ketoacidosis, some practical precautions should be taken in the presence of an infectious condition in a child or teenager with diabetes: - more frequent glycemic monitoring; - monitoring of ketones (serum or urine). It is important to remember that there are three types of ketone bodies: acetone,  $\beta$ -hydroxybutyrate and acetoacetate. In decompensation situations, the  $\beta$ -hydroxybutyrate/acetoacetate ratio varies from a normal 1:1 to 10:1. Most urine ketone strips, as well as laboratory measurements, measure only acetoacetate and can mask the presence of ketones in the blood, limiting the perception of metabolic deterioration. For this reason, in such cases of infection, it is best to use strips with reagents that measure  $\beta$ -hydroxybutyrate in the blood;

- regulation of the insulin dose - most often an increase in the insulin dose of insulin is required by 10-30%;
- the establishment of a ban on stopping taking insulin completely, even if the patient does not take food, since insulin is necessary for the basic metabolism, which can even increase in stressful situations;
- maintaining hydration with sufficient sodium and water [10].

When including infected patients in the treatment regimen who require special attention and monitoring of blood glucose levels, it is important to single out patients with diabetes associated with cystic fibrosis. Cystic fibrosis is the most common autosomal dominant disease among Caucasians, which is determined mainly by the clinical picture of recurrent infections and progressive loss of pulmonary function. This disease is usually easy to control, but it requires insulin therapy as a treatment, and pediatricians should be aware of the need for more intensive intervention during hospitalization due to pulmonary exacerbations when there is a need to increase the dose of insulin.

Vaccination of children with diabetes is the most important strategy for reducing morbidity and mortality from infectious diseases. Infections also cause complications of diabetes, such as hypoglycemia.

Some diseases prevented by the immune system are more common and more severe in patients with diabetes mellitus. In addition to pneumococcal infections and influenza infections, these patients are also potentially susceptible to hepatitis virus infection as a result of procedures related to the treatment and control of the disease, in particular, monitoring of glucose levels in capillary blood. Studies show that adult patients with diabetes mellitus are 1.5-2 times more likely to suffer from hepatitis B compared to patients of the same age group without this disease.

The usual regimen for immunocompetent people consists of three doses with an interval of one month between the first and second dose and six months between the first and third dose (zero, 1 and 6 months of life). The hepatitis B vaccine can be administered simultaneously or at any interval with other vaccines provided by the immunization program for all age groups.

In patients with diabetes mellitus, it is recommended to conduct a serological study (anti-HBS) 30-60 days after the last dose. Those who do not respond with an adequate level of antibodies should be revaccinated with three additional doses of the vaccine. Those who remain negative anti-HBS after two complete three-dose regimens should be considered immune and susceptible in case of exposure.

The flu vaccine should be used annually, starting from the age of 6 months. Children under the age of 9 receiving the vaccine for the first time need two doses at intervals of four to six weeks. One annual dose is enough for subsequent vaccinations.

Decavalent pneumococcal vaccine (PCV10) can be administered at the age of 2 to 59 months.

The vaccine against *Haemophilus influenzae* type b is offered at the age of 2 months to 19 years.

Despite the increased risk of vaccine-preventable diseases and international vaccination recommendations, several national studies have shown that the coverage of childhood patients with diabetes with vaccines recommended by

immunization programs is below optimal, which indicates the vulnerability of this group to a significant range of preventable diseases, as well as the need to strengthen immunization strategies for these patients. Such a decrease in vaccination rates seems to be a global phenomenon, including in the children's age group. Studies have shown that the vaccination rate in children with diabetes is lower than in healthy children and even in children with other chronic diseases, while the absence of a vaccine in the body of such patients can lead to various complications.

## 5. CONCLUSIONS

Children with diabetes have some disorders of the immune system, which, combined with high glycemia, increase the risk of infections and their severity, and they should be immediately detected and treated. The presence of an infectious condition, in turn, increases blood glucose levels and increases the risk of decompensation, so pediatricians should be warned against the need to strengthen monitoring and insulin therapy. Patients with diabetes are often not fully vaccinated against various diseases. Vaccines are vital for these patients, significantly reducing the risk of infections and exacerbating the development of the underlying ailment.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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