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RESEARCH ARTICLE

VIRAL INFECTION, ENVIRONMENTAL FACTORS AND DYSBIOSIS IN THE AUTOIMMUNE NATURE OF TYPE 1 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

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Abstract

A review of literature sources covering the autoimmune nature of the initiation and development of type 1 diabetes mellitus depending on viral infections, environmental factors and developing intestinal dysbiosis. The possibility of a protective effect of viral and bacterial infection, as well as vaccination is discussed.

Introduction:-

The United Nations has recognized that it is the first and only non-communicable disease to become an epidemic in the 21st century [33].

The autoimmune mechanism in the pathogenesis of type 1 diabetes convincingly demonstrates the close relationship between the regulatory activity of the triad: nervous, endocrine and immune systems. The detection of autoantibodies to antigens of pancreatic islet beta-cells, in particular, to insulin (IAA), glutamate decarboxylase (GADA), islet antigen-2 (IA-2A), zinc transporter 8 (ZnT8A) and tetraspanin-7 confirms the possibility of using them as reliable markers of neuro-endocrine-immune interactions in autoimmune diabetes mellitus [8, 12, 14, 35, 60, 74, 108]. In the course of the development of autoimmune reactions in relation to the islet tissue, the spread of this reactivity to other target autoantigens and epitopes is manifested. In the age aspect: autoantibodies to insulin are often the first autoantibodies formed in infancy, followed by antibodies to glutamate decarboxylase, while antibodies to islet antigen-2 and zinc transporter 8 are detected later [80, 116].

The pathogenesis of type 1 diabetes mellitus in genetically predisposed patients is also based on complex interactions between environmental and genetic factors. A serious complication of the autoimmune processes that cause T1DM is damage to other organs, which results in the development of additional autoimmune diseases in patients. These complications include autoimmune thyroid disease, celiac disease, and autoimmune gastritis. Diabetes can be a component of polyglandular autoimmune syndrome [55].

Currently, type 1 diabetes is becoming the most common chronic disease in the young population under the age of 18 years. In industrialized countries and in developing countries, there are characteristic differences in the incidence of type 1 diabetes mellitus [55].

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The fact that, precisely, autoantibodies cause the destruction of pancreatic beta-cells remains unproven. However, there is a lot of evidence of the autoimmune nature of the pathogenesis of type 1 diabetes mellitus. Obviously, the etiopathogenesis of this disease is complex and multifactorial. Most likely, the development of the disease is caused by the presence of many factors that initiate and modulate the immune response [6].

Genes of the major histocompatibility complex (MHC) on chromosome 6p21.3 provide a genetic predisposition to the development of type 1 diabetes [55]. Polymorphisms or mutations in many other genes also determine predisposition to type 1 diabetes. The insulin gene promoter (INS-VNTR, the gene encoding the T-lymphocyte activation receptor (CTLA-4, T-lymphocyte cytotoxic antigen 4) and the N22 tyrosine phosphatase gene protein (PTPN22, protein tyrosine phosphatase, non-receptor type 22) are extremely important for the formation of predisposition [48].

However, the main influence on the increase in the incidence of type 1 diabetes observed in the last decade is exerted by environmental factors. Genetic factors cannot act for such a short time [54, 78]. Interestingly, T1DM is often diagnosed in patients with a low genetic predisposition. Environmental factors are the main trigger initiating the disease. This trigger acts by stimulating an immune response against beta-cells or by weakening protective mechanisms [49, 93]. Environmental factors that contribute to the development of autoimmune reactions in relation to cells of the islet tissue have not yet been established [48]. Among such important environmental factors in the pathogenesis of T1DM, the intestinal microbiota is distinguished. Dysbiosis in the intestine can play a significant role in the mechanism of progression of autoimmune damage to β-cells, as well as in the mechanism of initiation of the pathological process [54]. Such trigger environmental factors include viral infection of the body, especially against the background of vitamin D3 deficiency. Infection with various viruses induces the development of autoimmunity in pancreatic beta-cells [92]. Until 90% of the beta-cells of the islet tissue of the pancreas are destroyed before destruction, a subclinical period of the disease (prediabetes) is isolated until clinical symptoms appear. It is the subclinical period that is characterized by the onset of an autoimmune response and the appearance of autoantibodies, sometimes many years before the manifestation of the disease [115].

During the diagnosis of the disease in children and adolescents, autoantibodies are detected: to glutamic acid decarboxylase (anti-GAD), to islet cells (ICA), to insulin (IAA), to tyrosine phosphatase (IA2), and antibodies against zinc transporter 8 (ZnT8). These antibodies play a key role in diagnosing the autoimmune nature of diabetes mellitus and in determining the severity, risk of progression, and predicting the symptomatic phase of the disease [17, 58]. Unfortunately, organ-specific autoimmune diseases can occur as a result of the progression of autoimmune damage to beta cells of the pancreatic islet tissue [51].

Hashimoto's thyroiditis and Graves' disease are the most common comorbidities in type 1 diabetes and are collectively referred to as autoimmune thyroid diseases. The pathogenesis of celiac disease, autoimmune gastritis/pernicious anemia, Addison's disease and vitiligo can also be induced by organ-specific autoimmune reactions associated with type 1 diabetes. In children and adolescents of patients with T1DM, the incidence of these diseases is significantly higher than in healthy individuals [9, 102].

The regulation of inflammatory reactions, prevention of a decrease in the proportion of populations of beta-cells in the islet tissue of the pancreas or a violation of their functions is determined by the following key factors: $CD4^+$ $CD25^+$ $FoxP3^+$ (Treg) T-cells, which play an important role in the regulation of the inflammatory response in the islet tissue of the pancreas [77, 88, 90, 110]. These factors maintain a balance between the action of inflammatory cytokines, on the one hand, and the tolerance of the immune system to its own tissues, on the other hand [56].

There is no doubt that genetic, immunological and environmental determinants increase the risk of initiation and development of type 1 diabetes mellitus. The action of these putative factors is mainly determined by the Human Leukocyte Antigen (HLA) genes located on chromosome 6. Among these factors are viral infections; parotitis; geographical location; family history; diet stressful influences; perinatal exposures and various autoimmune conditions (Hashimoto's thyroiditis, multiple sclerosis, pernicious anemia, Sjogren's syndrome, idiopathic thrombocytopenic purpura, vitiligo, dermatitis herpetiformis, Addison's disease and systemic lupus erythematosus).

During the diagnosis, the clinical symptoms of the disease can be detected later only after a significant reduction in the proportion of β-cells to about 30% of the cells. Even with clinical symptoms, patients maintain some ability to regenerate β-cells for decades after the onset of the clinical picture. With such a clinical picture, autoimmune

reactions continue the destructive effect on β-cells of the islet tissue of the pancreas in parallel with regenerative processes [61]. Most studies are aimed at identifying the role of immunological and metabolic factors in ensuring pathogenesis and establishing remission [72].

It should be taken into account that patients with T1DM have an increased risk of initiation and development of autoimmune thyroiditis and celiac disease [10, 41]. Carrying out therapeutic measures to improve glycemic control in children and adolescents with T1DM can reduce the risk of developing organ-specific autoimmune diseases, microvascular complications of diabetes, and also prevent the onset of short-term and long-term complications [65].

Analyzing thousands of stool samples taken from hundreds of infants and children followed from birth as part of the TEDDY studies, once again proved the link between viral infection of the body and the development of autoimmunity against pancreatic islet beta-cells. The identification of specific viruses in fecal samples has provided new data on the relationship of various types of enterovirus (Coxsackievirus) with the autoimmune nature of the pathogenesis of type 1 diabetes. It was expected that short-term infection is associated with autoimmunity of pancreatic islet beta-cells, but it has been found that long-term infection lasting more than 30 days may also underlie autoimmunity [104].

The hypothesis of a viral infection that initiates and enhances autoimmune responses to pancreatic islet tissue cells is becoming quite popular. Destructive processes in β-cells are associated with the presence of viruses in the tissues of the pancreas in diabetic patients. Increased morbidity due to respiratory infections in children is accompanied by the development of T1DM and an increase in the titer of specific autoantibodies to pancreatic islet tissue lectks in early adolescence [59]. However, respiratory infections with adenovirus C in early age periods are accompanied by a decrease in the risk of developing autoimmunity. The mechanism of such a protective effect of adenovirus C at an early age in relation to autoimmune reactions against beta-cells of the pancreatic islet tissue is not fully understood.

It is noteworthy that adenoviruses on the membrane surface of beta-cells are perceived by the same receptors as the Coxsackie B virus. Beta-cells show a high degree of expression of membrane receptor genes for adenovirus (CXADR) and Coxsackievirus, which can contribute to enterovirus infection [100]. This fact may provide a key to explaining the mechanism of interaction between viral infection and pancreatic islet tissue cells [104]. Increasing evidence is accumulating that viruses are involved in the autoimmune destruction of pancreatic islet β-cells, leading to deficiency in insulin biosynthesis and secretion and type 1 diabetes [57, 97, 112]. The high rate of viral mutations, the cyclic periodicity of viruses [1], and the survival of variants with altered pathogenicity and the ability to spread in populations create a great obstacle to convincing evidence of a close relationship between infection with RNA viruses and autoimmune morphological and functional changes in the islet tissue of the pancreas.

Studies conducted *in vitro* on human pancreatic islet tissue cell cultures demonstrate significant differences in the virulence of enteroviruses against beta-cells between serotypes and within the same serotype [84, 85]. Prolonged and repeated infections with enterovirus B are likely to be closely involved, namely, in the mechanism of initiation and development of islet autoimmunity. Even less frequent infections with mastadenovirus C in children at an early age correlate with manifestations of pancreatic islet tissue autoimmunity [104].

Autoreactive $CD4^+$ and $CD8^+$ T-cells that recognize pancreatic antigens can have a damaging effect on insulin-producing beta-cells. The main driving force behind the progression of type 1 diabetes is considered to be infiltration of the islets of Langerhans, where beta-cells are known to be localized. This islet infiltrate in humans consists mainly of $CD8^+$ T-cells and B-cells, as well as macrophages and dendritic cells of various subtypes. Islet infiltrate has a rather powerful destructive effect on the beta-cells of the islet tissue of the pancreas, which is difficult to stop [47].

Most of the evidence in favor of a connection with the autoimmune mechanism of the development of type 1 diabetes is for a spectrum of viral infections, including enteroviruses, in particular, Coxsackie B virus (CVB) [45], as well as rotavirus [38, 39], mumps virus [44] and cytomegalovirus [73]. CVB4 is the most common enterovirus strain found in individuals with pre-diabetic and diabetic syndrome. In diagnostics, it is possible to detect CVB RNA in the blood of patients at the onset and during the development of type 1 diabetes [3, 19]. Additional evidence was obtained in vitro using isolates of enteroviruses taken from newly diagnosed patients with type 1 diabetes. These isolates induce destructive processes in beta-cells of the islet tissue of the human pancreas [26]. CVB4 infection induces an inflammatory process in the islet tissue of the pancreas, which is mediated by natural killer (NK) cells

within the islets [23]. Receptors for the action of enteroviruses on the membrane surface of beta-cells are poliovirus receptors and integrin αvβ3. Both of these receptors are expressed by beta-cells of the pancreatic islet tissue [113].

The seasonal nature of enteroviral infections is proved by the corresponding fluctuations in the level of autoantibodies in children genetically predisposed to diabetes [53]. It has been suggested that the rubella virus also causes type 1 diabetes. So far, only congenital rubella syndrome has been associated with this T1DM [22, 31, 64].

It is noteworthy that an increased titer of antibodies to enteroviruses is found in pregnant women, whose children later develop type 1 diabetes mellitus [42].

Data from studies performed on migrants allow evidence of the involvement of environmental factors in the pathogenetic mechanisms of type 1 diabetes mellitus, since the diagnosed incidence in migrating populations seems to correspond to the typical incidence of the region to which migration occurs [16].

Thus, those viral infections that cause severe inflammation in the islet tissue of the pancreas may represent the first step in the chain of mechanisms for inducing autoimmunity and type 1 diabetes mellitus. Viral infection makes beta cells more open to recognition by $CD8^+$ T-cells by stimulating interferon production and activating major histocompatibility complex (MHC) Class I protein biosynthesis [29].

Congenital infections have been proposed to explain the development of type 1 diabetes in offspring. Thus, the use of antimicrobials by mothers before pregnancy and subsequently by the child was associated with a higher risk of developing type 1 diabetes [52].

A decrease in infection rates contributes to an increase in the incidence of type 1 diabetes without supporting the role of viruses in inducing the disease. A decrease in the frequency of infection may lead to an increase in susceptibility to the action of diabetogenic viruses [105, 106]. Exposure to viruses is not necessarily the cause of type 1 diabetes and may even be beneficial in some cases. The immune system can be trained to better cope with inflammatory diseases, often being exposed to inflammatory processes during life [29].

However, there is another hypothesis that a viral infection may have a preventive effect and alleviate the course of type 1 diabetes. A decrease in the incidence of type 1 diabetes is observed in countries with a lower socioeconomic status, which is associated with a higher infection rate. This phenomenon may also be associated with the use of certain vaccination strategies in countries with different sanitary standards [29].

Vaccination that attenuates viral infection of the islets may provide protection against type 1 diabetes through stronger immunity to diabetogenic enterovirus infections [50]. The incidence of type 1 diabetes mellitus reached a plateau 6 years after the introduction of the vaccine against mumps, measles and rubella [43].

Viral infections appear to have both deleterious and protective effects on the development of type 1 diabetes, which may depend on the nature of the virus as well as the immune status of the host and thus the time of infection [29].

It is noteworthy that children with Down syndrome and type 1 diabetes mellitus have an increased titer of antibodies to glutamate decarboxylase (GADA) [32]. It is assumed that Down's Syndrome may contribute to the pathogenesis of diabetes of an autoimmune nature, especially in the early periods of postnatal individual development. An interesting observation in this study was that children with Down's Syndrome and diabetes used less insulin but showed better glycemic control [32].

The fundamental understanding of how viral or bacterial infections, vaccination or dietary habits, and stressful situations determine autoimmune responses in certain individuals is currently very relevant. Importantly, environmental and climatic factors may play a triggering role in the development of autoimmune diseases. The transition from eustress to distress and the intensification of stress damaging effects are determined by polymorphic genes of the immune response, both innate and adaptive [79, 89, 111].

The body's fight against infection is determined by innate immunity genes, while the progression of viral or bacterial infection to overt autoimmune disease appears to be determined by adaptive immunity genes. It is important that some genes of the innate and adaptive immune response can have not only pro-inflammatory, but also anti-

inflammatory and immunosuppressive effects. This effect depends on age, sex, target cells and the nature of the immune response trigger. For example, rubella virus can directly infect pancreatic islet beta-cells and, as a result, reduce insulin biosynthesis and secretion, providing experimental evidence of the trigger role of rubella virus infection in the pathogenesis of T1DM [103]. Rubella infection at birth from infection during maternal pregnancy has been shown to increase the risk of developing T1DM in genetically predisposed newborns [15]. Namely, in these patients with congenital rubella and the manifestation of progression of type 1 diabetes, the antigens HLA-DR2 and HLA-DR3 are detected. Such viral infection with rubella at birth provides a clear example of how perinatal exposures can have a triggering effect on patients with a genetic predisposition to T1DM.

Autoimmunity is triggered by rotavirus infection, which is considered the most common cause of gastroenteritis in children. Rotaviruses share homologous amino acid sequences with two type 1 diabetes autoantigens: glutamic acid decarboxylase (GAD) and protein tyrosine phosphatase (IA2). Such molecular mimicry determines the autoimmune reaction [15]. Early diagnosis of type 1 diabetes made it possible to demonstrate that infection with enteroviruses (Coxsackie B virus, CBV) is characterized by the presence of specific IgM class antibodies against the CBV antigen. Such viral infection is also associated with an increase in the titer of antibodies to beta-cells of the pancreatic islet tissue and antibodies to insulin [37]. In the family, when comparing brothers and sisters in children and adolescents with T1DM, an increased titer of serum IgM antibodies is found. While immunopositivity to tumor necrosis factor-alpha (TNF-α) in children and adolescents with T1DM at the onset of the disease is significantly lower than in individuals in the control group [25].

Rapid initiation and pathogenesis of T1DM can be detected during infection with cytomegalovirus (CMV) [36]. Infection with the mumps virus in children and adolescents with mumps is associated with the development of T1DM against the background of an increase in the titer of antibodies to cells of the islet tissue of the pancreas. *In vitro* studies have shown that the mumps virus infects human β-cells and triggers an autoimmune response mechanism that causes the induction of type 1 diabetes mellitus [103]. A significant increase in the incidence of type 1 diabetes in children and adolescents causes infection with two or more of the above-mentioned viral infections. Repeated and combined viral infection accelerates the pathogenesis of T1DM [2]. There is evidence for this, which demonstrates that a history of serious infections in early childhood (pneumonia, abscesses, and meningitis) significantly increases the risk of T1DM. Inflammatory mediators (various cytokines) also accelerate the pathogenesis of T1DM and worsen the course of an autoimmune process that has already begun [98].

Another interesting hypothesis is the induction and development of T1DM by infection with *Mycobacterium avium* subspecies paratubercolosis, John's disease in cattle in cases of consumption of cow's milk of sick animals [24].

An interesting alternative conceptual approach to revealing the mechanisms of initiation and pathogenesis of DM1 is the so-called “hygienic theory” [30]. It turns out that in socio-economically developed countries, compared with low-income countries, there is a higher incidence of type 1 diabetes. This looks very contradictory, since in countries with low incomes and poor infrastructure, household overcrowding and poor sanitary quality of food and drinking water are formed [7].

Infection with human masadenovirus-C (HAdV-C) shows a correlation with a decrease in the frequency of autoimmune reactivity. This may be due to competitive inhibition by the HAdV-C virus, involvement of adenovirus receptors (CAR), or sustained activation of innate immunity leading to protection against other strains of the virus, including enterovirus [59].

In favor of the "hygienic theory" and speak data obtained from an animal model (in mice with diabetes without obesity, NOD). When these animals are infected with bacteria (*Mycobacterium bovis* or *Mycobacterium avium*) in early age periods, the onset and development of diabetes mellitus is prevented [87]. Even bacterial extracts have such a protective effect, proving that the microflora does not have to be alive. Prevention of diabetes development by infecting NOD mice with *Schystosomamansoni* proves the possibility of modulating autoimmune reactivity in this way [114].

The “hygienic theory” is explained by the fact that the immune response to infectious agents is associated with a high degree of proliferation and differentiation of regulatory T-cells (suppressor cells), which suppress other immune responses, including autoimmune ones. *Schystosomamansoni* infection in NOD mice presumably prevents the development of diabetes by modulating autoimmune reactivity [114].

Thus, an increase in the frequency of occurrence of multiple autoimmunity in young patients with T1DM is determined by the general genetic background, immunoregulatory deficiency, environmental triggers, changes in the balance of the intestinal microbiota, and epigenetic modifications induced by air pollutants. The rise in autoimmune diseases also coincides with the rising prevalence of obesity among young people [63].

Monogenic multiorgan autoimmunity requires early diagnosis, since the etiopathogenesis, natural course, and relief of these conditions differ significantly in individuals. It also requires the use of a large cohort of surveyed children and adolescents with T1DM to study the nature of monogenic conditions [96].

Organ-specific autoimmune diseases, such as autoimmune thyroiditis and celiac disease, are serious complications of type 1 diabetes. However, long-term complications, characterized by damage to the eyes, kidneys, central and peripheral nervous system, are also of paramount importance for the severity of the disease and the possibility of a cure [70].

It is possible to reduce the risk and delay the development of microvascular complications of diabetes by improving the glycemic balance in children and adolescents with type 1 diabetes [70]. Obviously, the effectiveness of glycemic control and balancing of hemoglobin A1C (HbA1C) levels is largely determined by the age of patients. For example, older patients show worse glycemic control and elevated HbA1C levels [67]. According to similar studies, HbA1C levels in adolescents are significantly higher than in young children [67, 91, 101]. In addition to the age aspect, it is necessary to take into account the presence of suffering from psychosocial and family problems, a decrease in the degree of daily physical activity, changes in the hormonal profile, manifestations of increased insulin resistance during puberty, as well as the progressive nature of the disease [67].

Metabolic biomarkers may provide clues to the classification of type 1 diabetes subtypes, of which there are at least two. These subtypes are determined by genetic factors and immune phenotypes. HbA1c-based diagnosis in children, adolescents, and adults has varying predictive value for assessing the progression of clinical diabetes from childhood [86].

A significant part of the genetic risk for the induction and course of the pathogenesis of type 1 diabetes is due to the Human Leukocyte Antigen (HLA) and insulin genes. Many polymorphic genes, including PTPN22, IFIH1, CTLA4, and IL2RA, have been identified in the study of autoimmune reactions [11, 109]. Viral infections are a serious provoking factor for intestinal pathologies and the formation of dysbiosis. Numerous viruses, especially those associated with intestinal pathologies, are also associated with the pathogenesis of T1DM, including enteroviruses, rotaviruses, cytomegaloviruses, and noroviruses [36, 75, 76, 83]. Enterovirus Coxsackie B virus (CVB) is most commonly associated with T1DM. Imbalance of the intestinal microbiome and formed dysbiosis, which are observed in patients with viral infection, lead to autoimmune damage to beta cells of the pancreatic islet tissue, induction and development of type 1 diabetes mellitus [68]. It has already been shown that shifts in the composition of the gut microbiome, dysbiosis, exposure to dietary antigens, and vitamin D deficiency significantly influence the susceptibility of children and adolescents to T1DM [28, 81]. Long-term enterovirus infections in patients with type 1 diabetes mellitus are associated with serious disorders in the intestinal mucosa, leading to the development of a persistent inflammatory process. Leaky gut, mild enteropathy, and a dysbiotic microbiome often occur in patients with autoimmune damage to pancreatic islet beta-cells. In this state, there is also a pronounced jump in the expression and biosynthesis of Coxsackievirus and adenovirus (CAR) receptors in the insulin-secreting beta-cells of the pancreatic islets [46, 104].

It is indicative that in the course of diagnosis, a correlation of seasonal fluctuations in infection with manifestations of DM1 and other autoimmune diseases is revealed [66, 68].

Early loss of tolerance of B-lymphocytes to insulin can be represented in the mechanism of weakening humoral protection against Coxsackievirus infection. While an increase in autoantibody titer to the T1DM biomarker (glutamic acid decarboxylase, GAD) is associated with a fairly competent response to CVB infection, proving that virus clearance can be altered in people with T1DM [5]. Against the background of dysbiosis due to rotavirus infection in children, the genetic predisposition to DM1 significantly aggravates autoimmunity and the course of diabetes [68]. However, the acceleration of the development of the disease is clearly manifested in the case of early autoimmune reactions [34]. Obviously, activation of autoimmune response pathways and interaction with innate viral receptors play an important role in the initiation and pathogenesis of T1DM [68, 97]. Intestinal dysbiosis,

elevated levels of interferon markers and viral signatures (enteroviral protein and double-stranded RNA, dsRNA) are associated with autoantibody immunopositivity in pancreatic islet tissue in recent T1DM patients [4]. Whereas temporarily deleted viral genomes show the ability to persist in the microenvironment of the islet tissue, causing inflammation and increased recruitment of immune cells [68].

Direct connections of the inflammatory process induced by viral infection with the modulatory effect on immune responses in the islet microenvironment have already been proven. There is also a high probability of secondary effects of viral infection, which underlie the long-term influence on the pathogenesis of type 1 diabetes, in particular, in microbial dysbacteriosis [68]. The human microbiome is, of course, rather heterogeneous and its influence on the processes of initiation and development of type 1 diabetes mellitus is not unambiguous. However, in patients with T1DM and islet autoimmunity, certain microbiome shifts are revealed towards the predominance of a marked decrease in the diversity of bacteria that colonize the intestine, an increase in the proportion of bacteria of the *Bacteroides* type, a decrease in the proportion of *Firmicutes* representatives, and a decrease in the production of short-chain fatty acids (SCFAs) by intestinal microbes [20, 27, 54, 62]. Namely, during the first few years of postnatal life, colonization of the gastrointestinal tract plays a determining role in the formation, maintenance, and fine regulation of the immunity of the host macroorganism [82, 94]. After passing through infancy, the microbiome appears to stabilize with relatively well-established communities of microorganisms that continue to form immune homeostasis into adulthood [13]. With age, the microbiome exhibits a decrease in the degree of plasticity and tolerance to all sorts of new effects of antigens and environmental factors [21, 82]. This weakening of plasticity is an important factor determining the likelihood of dysbiosis and concomitant impact on the autoimmune nature of type 1 diabetes mellitus under the threatening effect of the environment [68].

Conclusions:-

1. An increase in the frequency of occurrence of multiple autoimmunity in young patients with T1DM is determined by the general genetic background, immunoregulatory deficiency, environmental triggers, changes in the balance of the intestinal microbiota, and epigenetic modifications induced by air pollutants. The rise in autoimmune diseases also coincides with the rising prevalence of obesity among young people.

2. Direct connections of the inflammatory process induced by viral infection with the modulatory effect on immune responses in the islet microenvironment have already been proven. There is also a high probability of secondary effects of viral infection, which underlie the long-term influence on the pathogenesis of type 1 diabetes, in particular, in microbial dysbacteriosis

3. Colonization of the gastrointestinal tract plays a determining role in the formation, maintenance, and fine regulation of the immunity of the host macroorganism during the first few years of postnatal life. The microbiome exhibits a decrease in the degree of plasticity and tolerance to all sorts of new effects of antigens and environmental factors with age.

4.Vaccination that attenuates viral infection of the islets may provide protection against type 1 diabetes through stronger immunity to diabetogenic enterovirus infection.

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