13. *Тимошко М.А., Надводнюк А.И., Хайдарлиу С.Х.* Влияние импульсных воздействий температуры на функциональное состояниепоросят раннего возраста. //ИзвюАН МССР Сер.биол. и хим.наук. – 1984. – 2:72-73.
14. *Фурдуй Ф.И.* Пролблемы стресса и преждевременной биологической деградации человека. Санокреатология. Их настоящее и будущее. В: Современные проблемы физиологии и санокреатологии. – 2005. – с.16.

## THE ROLE OF COXSAKIE VIRUS IN THE DEVELOPMENT OF TYPE I DIABETES MELLITUS

**Emilia Ţîmbalari, Serghei Covanţev**
Department of Microbiology, Virusology and Immunology, USMF "Nicolae Testemiţanu"

**Summary**

Coxsackie virus is a member of Enterovirus genus with high prevalence among population. Recent data indicate that this virus may partially be responsible for the incidence of type I diabetes. Taking in consideration the 5.3% increase of diabetic patients per year, every possible cause should be taken in consideration. A review of studies of Coxsackie viruses regarding their possible role in the development of type I diabetes is presented in this article.

**Rezumat**

***Rolul virusului Coxsakie în dezvoltare diabetului zahărat de tip I***

Virusul Coxsackie este un membru de genul Enterovirus cu prevalenţă înaltă în populaţie. Date recente indică faptul că acest virus poate fi parţial responsabil pentru incidenţa de diabetul zahărat de tip I. Luînd în considerarea că creşterea pacienţilor cu diabetul zaharat este 5.3% anual fiecare cauză ar trebui să fie luată în considerare. În acest articol este prezentată o revizuire a studiilor de virusuri Coxsackie privind la rolul acestora în dezvoltarea de diabetul zaharat de tip I.

**Intoduction**

Coxsackie viruses have been described in the 1948-49 by Gilbert, a researcher from New York. He discovered them from the intestine of children with poliomyelitis-like disease. G. Dalldorf with G. Sikls were looking for a method of treating polio. Despite the complete morphological similarity with polio virus, Coxsackie viruses have a different antigenic structure. A new family of viruses has been given the name Coxsackie, on behalf of a small town in the state of New York, where G. Dalldorf identified the first strains from fecal samples.

Coxsackie virus belongs to the picornavirus family, genus Enterovirus. It has 4 protein forming the capsid about 30 nm long, which surrounds a single RNA molecule the size of 7.5 kb. Coxsackie viruses are divided into two groups A and B. Group A consists of 23 serotypes. The B group consists of at least 6 serotypes. Of these groups A9, B1, B2, B3, B4, B5 are considered to be related to first type of diabetes [1, 2, 3].

Coxsakie viruses have a broad area of distribution and high levels of morbidity in the population, especially in the warmer months. Depending on the patient's age and serotype of the virus the sickness rate varies from 2-100%. It is important to mention that 60% of patients have subclinical presentation of the disease. Coxsackie virus is one of the most common virus infections after polio virus [1].

Recent years are marked with the increased number of evidence in favor that diabetes is a polietiological disease. The incidence of diabetes increases 5.3% per year. Overall incidence in the population varies between 1.6-30.9%, depending on the country. I type diabetes (T1D) is more common in young age. In 54-89% of such cases autoimmune process of β-cells is found.

The pancreas is an exocrine and endocrine organ. The endocrine part of the pancreas is presented by a group of cells that form islets of islets of Langerhans. Among these cells are the β-cells which play the key role in the development of T1D.

β-cells are the only cell type in the body capable of producing insulin. Insulin is a hormone with a wide range of metabolic effects. Insulin acts my several molecular mechanism thus supporting aminoacid, lipid and carbohydrate transport, storage etc. One of the most important functions of insulin is to provide glucose transport into cells. Without this hormone the use of glucose as an energy source is practically impossible, which causes an increase in blood sugar level - hyperglycemia, with all the attendant complications. Among the T1D complications are listed cardiovascular, neural and kidney pathologies. Patients with T1D have an increased chance of myocardial infarction, strokes and end stage kidney disease. This makes T1D an important cause of mortality and morbidity among the population.

**The possible pathophysiology of T1D**

The exact mechanism by which the β-cells are attacked by immune system is not known. But the current theory proposes that Coxsackie virus causes a persistent infection of β-cells that activates the immune system. The most important theories are the theory of bystander damage and molecular mimicry.

The theory of molecular mimicry is supported by the presence of similarities between Coxsackie virus protein 2C and β-cell protein GAD65. This leads to the synthesis of antibodies against a protein that is actively synthesized by the pancreas.

The bystander damage is another theory. Pancreatic cells infected by Coxsackie virus RNA can lead to pancreatitis, but due to the damage a large amount of cytokines is released by islets cells.

An alternative theory was recently proposed in which thymus is considered to be main organ affected by the virus. This can lead to the damage of T regulatory cells. The current data shows that infection can lead to thymus anomalies which can modify the tolerance of the body to its own cells. This can result in mutant T cells that cannot properly identify foreign pathogens from the cells of the organism. 89% of cases of T1D are autoimmune. This partially can be explained by abnormal T cells that play one of the dominant roles in pathophysiology of T1D [4, 5].

**Clinical presentations**

The incubation period for enterovirus infection is 2-35 days, an average of 3 to 12. Most infections are asymptomatic. Clinically significant symptoms are usually the same as the common cold. Enterovirus infections are the second most common causative agent of severe acute respiratory syndrome (SARS).

However, a small percentage of patients may have severe complications or other clinical manifestations of the disease. These may include serous enteroviral meningitis, herpangina, epidemic myalgia. Due to the fact that the main route of infection is through the gastrointestinal tract (GIT) Coxsackie viruses can cause enteritis with diarrhea and abdominal pain.

Coxsackie viruses are resistant to the acidity of the stomach and may be asymptomatic 6 weeks or more in the GIT. In some cases only virus RNA can be identified using PCR which indicates that the virus doesn't replicate properly and sometimes makes mistakes. This can further complicate diagnostic procedures.

The virus has the ability to infect up to 100 different types of tissues which makes it a highly contagious infection [6, 7].

**Discussions**

The theory that diabetes is associated with enteroviruses was proposed in 1969 (Gamble et al).

There are several reasons why T1D can be caused by enterovirus infections. Less than 10% of genetically predisposed people develop diabetes during their life.Concordance in homozygous twins is 30-50%.

The incidence of T1D increases in late summer and early autumn, at the peak of enteroviral disease. This leads to the suggestion that the development of T1D has not only genetic factors involved but also epidemiological [8].

According to I. Mena et al., 2000 up to 50% of children with autoimmune diabetes have antibodies to the Coxsackie virus, as well as 20-34% of patients with pancreatitis [9].

Several authors have noted an increase in the secretion of IL-10 and TNF-a by cells of the pancreas infected with Coxsackie viruses, which results in the inflammatory process, but not always in the destruction of b-cells. These b-cells sometimes lose the ability to respond to increased blood glucose levels [10, 11].

Studies of DAISY (The Diabetes and Autoimmunity Study in the Young) indicates that of the 140 children who were found to have antibodies about 50 became sick with diabetes in the period of 4.2 years.

E. Witso et al., 2007 indicates a high risk of enterovirus infections. Of the 113 newborns about 58 had enterovirus infections. PCR test detected the presence of RNA viruses in fecal samples in 11.3%. Of these, were allocated 22 different serotype, including a 4.8% B type [10].

M. Elfving et al., 2008 indicated an increased risk of developing diabetes for boys whose mothers were IgM positive for the virus. The same effect was seen in mice [11].

The group with diabetes was more likely than the control group to be tested positive for enterovirus RNA in their system. Often the test was positive for RNA, but not for the proteins of the virus, indicating virus replication errors. The result indicates that the majority of diabetes patients have long-term infection of the intestinal mucosa, which can lead to the development of the disease [12].

Nevertheless, not all Coxsackie viruses have the same effect on β-cells. So Coxsackie virus B3 besides autoimmune effect may in some cases make the body resistant to the development of diabetes in the case of B4 virus infection. This effect has led to a theory in which it was suggested that low hygiene levels can lead to an increased incidence of some of the Coxsackie virus infection. But due to certain favorable factors: time, period of infection, the presence of a co-infection could lead to the development of immunity to the virus, and thus the T1D caused by the Coxsackie virus.

This can explain why in some countries with a high level of hygiene may be more patients with T1D, such as in Finland and Sweden.

Additionally this can be used in future therapies against Coxsakie virus and thus can lower the chance of developing T1D.

**Conclusion**

In our work, we showed one of the possible reasons for increase in the incidence of diabetes. Different Coxsackie virus models show different impact on the development of diabetes.

Several authors indicate that this virus can cause autoimmune diseases, with reasonable data from clinical and experimental study. On the other hand, not all studies investigated a large number of patients. Other studies didn't compare the diseased patients with a control group of healthy individuals to lower the percent of mistakes.

A number of authors in their studies denied the relationship between Coxsackie virus and T1D. It should be noted that more detailed analysis of this problem can lead to more precise and accurate data.

There remain a number of very important subjects for discussion, such as whether the Coxsackie virus affects all the patients equally, or some of them have some type of immunity. These molecular mechanisms should be taken in consideration because they have the capability

of providing significant protection from the infection. If they exist then they should be used to reduce morbidity of T1D, even if the virus is responsible for only a small percentage of diabetes.

T1D can be adequately reduced, significantly facilitating lives of patients who might get a lifetime health improvement. Additionally this can positively affect the overall health in different countries with high incidence of T1D.

Another proposition is the development of a vaccine against the virus and specific antiviral therapy drugs. This can significantly reduce the current diabetes pandemic.

**References**


1. Ryan K. J., Ray C. G. Sherris Medical Microbiology, Fifth Edition. The McGraw-Hill Companies: 2010.
2. Strauss J. H. Ellen G. Strauss Viruses and Human disease. Academic Press: 2007.
3. Hendry E., Hatanaka H., Fry E. The crystal structure of coxsackievirus A9: new insights into the uncoating mechanisms of enteroviruses. Structure, 1999, vol. 7(12), p. 1527-38.
4. Jaïdane H., Sané F., Hiar R. et al. Immunology in the clinic review series; focus on type 1 diabetes and viruses: enterovirus, thymus and type 1 diabetes pathogenesis. Clinical and Experimental Immunology, 2012, vol. 168, p. 39–46.
5. Stene L. C., Rewers M. Immunology in the clinic review series; focus on type 1 diabetes and viruses: the enterovirus link to type 1 diabetes: critical review of human studies. Clinical and Experimental Immunology, 2012, vol. 168, p. 12–23.
6. [Kishkurno E. P., Amvroseva T.V. Enterovirus infection in children: clinical features, diagnosis, approaches to therapy. Medical emergencies, 2007, vol. 2(9).]
7. [Demin A., Netyosov S. Enterovirus infections: the variety of clinical manifestations. Bulletin SB RAMS, 2009, vol. 6(140).]
8. Dotta F., Censini S., van Halteren A. G. S. et al. Coxsackie B4 virus infection of b-cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. PNAS, 2007, vol. 104(12), p. 5115-20.
9. Mena, I., Fischer, C., Gebhard, J. et al. Coxsackievirus infection of the pancreas: evaluation of receptor expression, pathogenesis, and immunopathology. Virology, 2000, vol. 271, p. 276–288.
10. Witsø E., Palacios G., Cinek O. et al. High Prevalence of Human Enterovirus A Infections in Natural Circulation of Human Enteroviruses. J. Clin. Microbiol., 2006, vol. 44(11), p. 4095-4100.
11. Elfving M., Svensson J., Oikarinen S. et al. Maternal Enterovirus Infection during Pregnancy as a Risk Factor in Offspring Diagnosed with Type 1 Diabetes between 15 and 30 Years of Age. Experimental Diabetes Research, 2008.
12. Oikarinen M., Tauriainen S., Oikarinen S. Type 1 Diabetes Is Associated With Enterovirus Infection in Gut Mucosa. Diabetes, 2012, vol. 61, p. 687-91.


## CARACTERISTICA REACTIVITĂŢII IMUNE ŞI REZISTENŢEI PREIMUNE LA BOLNAVII DE TUDERCULOZA PULMONARĂ


**Inna Cucerenco, Alexandra Golubeva, Serghei Ghinda, Alexandru Cotici**

Catedra Microbiologie, Virusologie şi Imunologie USMF "Nicolae Testemiţanu",
IMSP IFP „Chiril Draganiuc"



**Summary**

***Characteristics of immune reactivity and pre-immune resistance in patients with pulmonary tuberculosis***

Tuberculosis is one of the main goals of worldwide infection control and a primary public health problem which continues to remain the disease with a high mortality rate and significant