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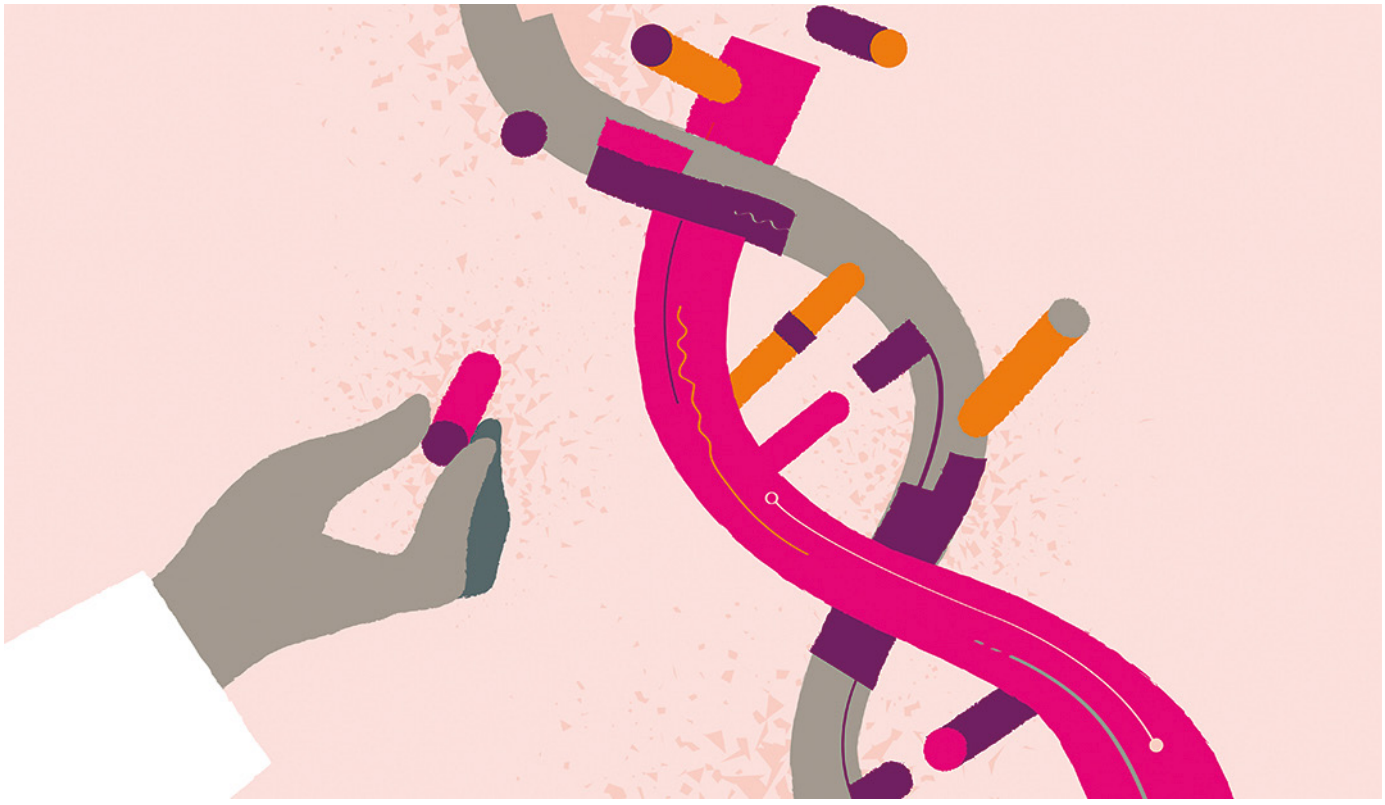

Enteroviruses and type 1 diabetes in children:

a relationship attracting scientific interest

Type 1 diabetes mellitus (T1DM) is a complex autoimmune disease characterized by the selective and progressive destruction of pancreatic β cells, which are responsible for insulin secretion. In general, it results from the interaction between genetic susceptibility and environmental triggers, which play an important role in its pathogenesis and development. Among these triggers, viruses have been implicated most consistently, particularly enteroviruses belonging to the Coxsackie B virus (CVB) group, because of their frequency, seasonal pattern—which resembles that of T1DM—their affinity or tropism for pancreatic tissue, and their ability to induce relevant immune responses. The convergence of a genetic risk profile for T1DM, viral infection, and autoimmunity causes failure of immune tolerance mechanisms, leading to the activation and infiltration of autoreactive cells that target pancreatic tissue *(Figure 1)*.

According to recent studies, CVBs remain the strongest **candidates as viral** triggers of T1DM. The available data reinforce the biological plausibility of this relationship and provide evidence supporting the concepts of persistent and/or repeated infection, specific immunological mechanisms, and potential preventive interventions. Nevertheless, the high prevalence of enterovirus infections in the general population, together with their variable and limited temporal association with T1DM, has made it difficult to establish a clear causal relationship.

Furthermore, the host's **variable immune response** to viral infection is highly relevant because it significantly influences whether and how such infection contributes to the development of T1DM in a given individual. In this regard, evidence indicates that the response to enterovirus infection differs in individuals at risk of developing T1DM.

This article summarizes the latest epidemiological, experimental, and mechanistic evidence supporting viral infection, **particularly CVB infection**, as a major trigger of the autoimmune process in T1DM. It also discusses the importance of the **genetic background** and the **individual immune response** according to age, together with the limitations of the available evidence and its potential future implications.

IS THERE STRONG EVIDENCE OF A RELATIONSHIP BETWEEN ENTEROVIRUS INFECTION AND THE DEVELOPMENT OF T1DM?

Overall **epidemiological evidence** consistently supports an association between enterovirus infection, particularly CVB infection, and the risk of T1DM. One of the main lines of evidence comes from cases of maternal viral infection during pregnancy and the subsequent detection of enteroviruses in the blood and stools of offspring, together with neutralizing antibodies against the virus. Second, a meta-analysis showed that enterovirus infection is associated with a significant 5- to 8-fold increase in the risk of T1DM, with a greater effect in children. Similarly, longitudinal collaborative studies »

THE HIGH PREVALENCE OF ENTEROVIRUS INFECTION IN THE GENERAL POPULATION AND ITS VARIABLE AND LIMITED TEMPORAL ASSOCIATION WITH T1DM HAVE PREVENTED THE ESTABLISHMENT OF A CLEAR CAUSAL RELATIONSHIP

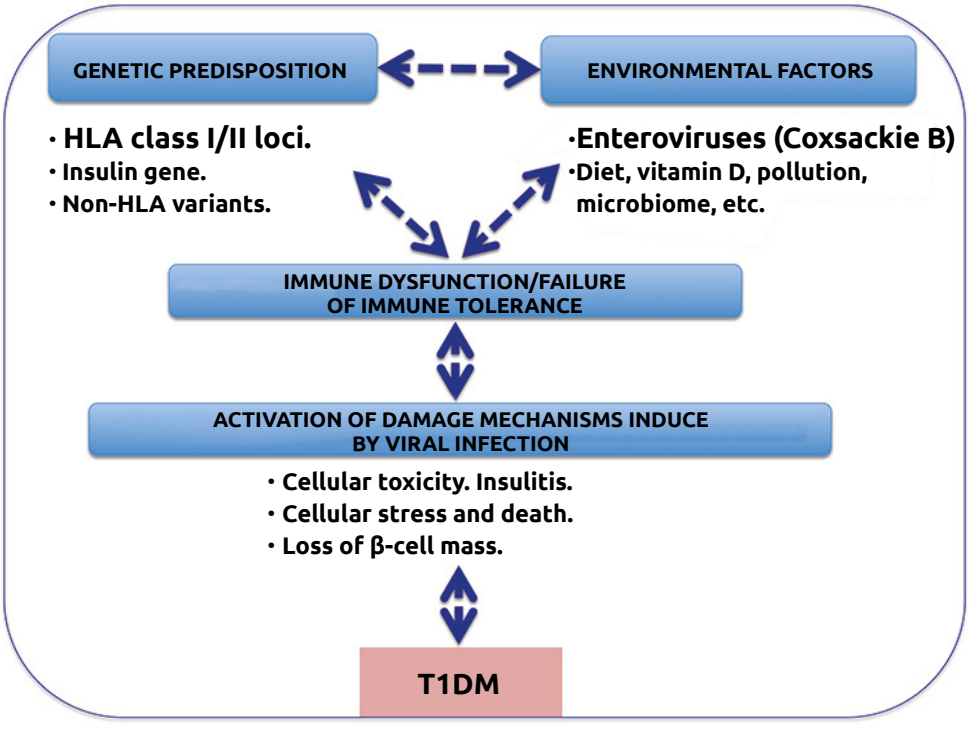

Figure 1

ENTEROVIRUS INFECTION, PARTICULARLY INFECTION WITH COXSACKIE B VIRUSES, IS A STRONG CANDIDATE TRIGGER OF T1DM AND MAY CONTRIBUTE TO THE INITIATION AND/OR ACCELERATION OF THE AUTOIMMUNE RESPONSE AGAINST PANCREATIC β CELLS

» conducted in Europe and the United States, such as TEDDY (The Environmental Determinants of Diabetes in the Young), indicate that CVB infection is significantly more common in patients with T1DM than in controls, particularly when sensitive molecular techniques such as reverse transcription polymerase chain reaction are used to detect viral genetic material. This study, together with others, suggests that persistent, recurrent, and/or chronic low-grade infection affects the pancreas—and not only pancreatic β cells—in T1DM, thereby supporting the association. Moreover, certain serotypes, such as CVB1, have been associated with the induction of islet autoimmunity before the clinical onset of disease. Both TEDDY and the DIPP (Diabetes Prediction and Prevention) study, conducted in the Finnish population, found a robust immune response to the virus in control children but not in children with pancreatic autoimmunity and positive autoantibodies.

Regarding the **temporal relationship between viral infection and progression to T1DM**, longitudinal cohort studies have shown that enterovirus infections precede autoantibody seroconversion in some individuals, suggesting a role during the initial phase of the disease. Nevertheless, the temporal relationship remains complex, and evidence indicates that multiple infections or repeated exposures may be required to trigger the autoimmune response against the pancreas. Overall, the epidemiological evidence provides strong support for an association, but it does not definitively establish causality.

With respect to the demonstration of **viral infection in tissues**, one of the most important advances in recent years has been confirmation of the presence of enteroviruses in human pancreatic tissue. Viral genetic material, particularly RNA, and capsid proteins have been detected in the pancreatic islets of patients with T1DM, both in postmortem samples and in biopsies from living patients. Recent studies confirm that CVBs can directly infect human β cells, with the simultaneous detection of viral RNA and increased expression of HLA class I genes in the islets. Moreover, infection is not confined to the pancreas; it has also been identified in the intestinal mucosa, suggesting the existence of a viral reservoir that may contribute to persistent infection.

Overall, these findings indicate that enterovirus infection, particularly infection with CVBs, is a strong candidate trigger of T1DM and may contribute to the initiation and/or acceleration of the autoimmune response against pancreatic β cells. Nevertheless, the main limitation to clearly establishing a relationship between enterovirus infection and T1DM is that most data come from epidemiological studies; therefore, a definitive causal relationship has yet to be established. Discrepancies also remain because not all studies have found a significant association. Some viruses may have protective effects, as proposed by the hygiene hypothesis, and differences exist among serotypes because not all CVBs are equally diabetogenic.

WHAT MECHANISM OR MECHANISMS ALLOW ENTEROVIRUS INFECTION TO DESTROY INSULIN-PRODUCING PANCREATIC β CELLS?

Current cumulative evidence supports a multifactorial model involving several interrelated mechanisms:

1. **Direct cellular injury (direct cytotoxicity).** CVBs can infect β cells and directly destroy them, releasing molecules that act as autoantigens and activate the adaptive immune response against them. Some studies have demonstrated direct cell death after viral infection in the presence of ineffective antiviral defense responses.

2. **Molecular mimicry (immune-system confusion).** Certain viral components resemble proteins expressed by pancreatic β cells and may confuse the immune response, thereby triggering cross-reactive autoimmune responses. This mechanism is well described in T1DM.

3. **Inflammation.** Viral infection activates the innate immune system, initiating an inflammatory cascade through the re- »

» lease of proinflammatory mediators and creating an environment that favors autoimmunity.

4. **Persistent infection or low-grade viral persistence.** In some cases, the virus is not completely eliminated and remains in the body, sustaining chronic inflammation that gradually damages β cells. This causes β-cell stress and dysfunction. Evidence indicates that CVB infection reduces insulin-gene expression and alters insulin secretion even before cell destruction occurs. Consistent with the previously cited DIPP study, the Diabetes Virus Detection Study (DiViD) has provided evidence of low-grade viral infection in the pancreatic tissue of patients with T1DM. Moreover, a recent study reported that 6 months of antiviral treatment helped preserve residual insulin production in children and adolescents recently diagnosed with T1DM.

5. **β-cell response to infection.** Pancreatic β cells themselves activate mechanisms that increase cellular stress and make them more visible to immune attack.

Overall, although the exact process by which CVB infection causes T1DM remains unknown, strong evidence supports several mechanisms—including direct injury, molecular mimicry, cellular stress, and evasion of immune defense mechanisms—through which viral infection may damage or even destroy pancreatic »

» β cells, eventually leading to the development of T1DM.

HOW DOES GENETICS INFLUENCE THE INTERACTION BETWEEN THE VIRUS AND THE INDIVIDUAL?

Not all individuals respond to viral infection in the same way. The **interaction between an individual's genetic background and viral infection** is a key factor explaining how genetic predisposition determines the way in which the immune system responds to a particular insult. Genetic factors therefore influence both susceptibility to infection and the immune response, which may explain why only a minority of infected individuals develop T1DM. In this context, some studies have shown a marked reduction or even absence of proteins with antimicrobial activity, known as defensins, in the pancreas of patients with T1DM compared with unaffected controls.

Furthermore, the **genetic susceptibility profile** for T1DM modulates each individual's immune response, directly linking genetic risk with the proinflammatory response to pathogens, including viruses. Approximately 40% to 50% of the genetic risk of T1DM is attributable to markers within the HLA system, particularly class II markers involving genes located in the DR, DQ, and, to a lesser extent, DP regions. These genes are essential for adaptation, immune-tolerance mechanisms, and immune-system responses. The next most important genetic risk factors include certain insulin-related genes, followed by other gene variants not linked to the HLA system. All these genetic variants—the individual's overall genetic burden—increase the vulnerability of essential regulatory immune mechanisms responsible for preventing autoimmunity. Once this barrier is breached, immune-response dysregulation and activation of certain T-cell populations occur. These defensive cells, including CD4+ and CD8+ T lymphocytes, are the principal effectors responsible for attacking and destroying the islets containing β cells.

Finally, one of the most interesting and still unresolved issues is the importance of the **timing of viral infection**, including prenatal exposure and infection during early childhood. It has been proposed that intrauteri- »

» ne infections may alter maturation of the fetal immune system and promote defective tolerance to pancreatic β-cell antigens. Some epidemiological studies also suggest that autoimmunity in T1DM begins very early in life and that susceptibility to immune dysfunction may therefore be programmed prenatally, creating a critical window for intervention.

WHAT ARE THE IMPLICATIONS OF DEMONSTRATING THAT ENTEROVIRUSES ARE LINKED TO THE DEVELOPMENT OF T1DM? COULD THE CONDITION BE TREATED?

A potential causal role of enteroviruses would indeed open new avenues for both prevention and treatment. The development of vaccines against Coxsackie B viruses represents one of the most promising strategies for preventing T1DM in at-risk populations. Another relevant approach would be risk stratification using combined viral and autoimmune markers, which could identify individuals during preclinical stages. Finally, targeted treatment with antiviral or immunomodulatory agents during the early stages could modify the natural history of the disease. Therefore, confirmation that enteroviruses—particularly Coxsackie B viruses—participate in the onset of T1DM would create new opportunities for prevention and treatment:

- Vaccines against Coxsackie B viruses to prevent T1DM in children at high genetic risk.
- Antiviral or immunomodulatory treatments to delay or halt β-cell destruction.
- Combined viral and antibody testing to detect the disease at an early stage. **D**

IN SUMMARY:

- Enteroviruses, particularly Coxsackie B viruses, are the viruses most closely associated with T1DM.
- They do not cause the disease by themselves, but they may trigger it in genetically predisposed individuals.
- The mechanisms involved include direct injury, inflammation, and an altered immune response.
- Research is ongoing, and a better understanding of this relationship may make it possible to prevent or delay disease onset in the future.

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