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Review

Type 1 diabetes and viral infections: What is the relationship?

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ABSTRACT

Type 1 diabetes (T1D) is the most common chronic metabolic disorder in children. Epigenetic and environmental factors capable of altering the penetrance of major susceptibility genes or capable of increasing the penetrance of low-risk genes are currently thought to play a role in triggering autoimmunity and T1D development. This paper discusses the current knowledge of the role of viruses in T1D. Most studies that have evaluated the potential association between viral infections and T1D have indicated that it is highly likely that some of these infectious agents play a role in T1D development. However, most T1D cases are immune-mediated, and it is supposed that the initial viral infection is capable of creating, in genetically predisposed subjects, a particular condition in which chronic local inflammation occurs through the persistence of the infecting virus in pancreatic tissue and the activation of autoimmunity by means of molecular mimicry, bystander activation, or both. Theoretically, this knowledge could lead to possible prophylaxis and therapy for T1D. Further studies devoted to evaluating which infectious agents are linked to T1D and which immune mechanisms induce or protect against the disease are needed before adequate prophylactic and therapeutic measures can be developed.

1. Introduction

Type 1 diabetes (T1D) is the most common chronic metabolic disorder in children. However, the incidence of childhood onset T1D varies significantly between and within countries, ranging from 0.1 cases in Venezuela to more than 40 cases in Finland per 100,000/year [1]. Lower incidence rates are observed in Asia, Africa, and Central and South America, whereas higher rates have been evidenced in northern Europe, North America, New Zealand, and Australia. In Italy, a single region — Sardinia —has a T1D incidence rate that is more than three times higher than that in other parts of the country (37.8 vs 10 per 100,000/year) [2]. In recent years, a significant increase in the number of new cases of T1D has been documented worldwide, particularly in very young children [3]. It has been calculated that T1D is increasing at a rate of ~3% to 5% per year [4].

TID is an autoimmune disease that is characterized by slowly progressing pancreatic beta-cell destruction, resulting in a reduction of insulin secretion and, over the course of several years, the development of clinically evident insulin-dependent diabetes mellitus [5]. The involvement of the immune system in disease development has been known for many years, as evidenced by the detection of antibodies that recognize pancreatic beta-cell components and insulin in the blood of individuals several years before T1D development [5,6]. Further confirmation of the autoimmune pathogenesis of T1D comes from evidence that, in patients with this disease, pancreatic islet infiltrates can be frequently detected, mainly due to CD8 and CD4 cells, B cells, and macrophages [7–11]. Alternatively, the transfer of bone marrow cells from T1D patients to healthy subjects can lead to disease development in the recipients [12], and the administration of immune modulators such as cyclosporine A and anti-CD3 monoclonal antibody can affect the disease, at least in the short term [13].

Many studies have demonstrated that T1D is a polygenic disease in which clinical manifestations are conditioned by different combinations of susceptibility genes. The major gene loci associated with susceptibility to T1D are within the human leukocyte antigen (HLA) region on chromosome 6. Class II alleles, in particular, specific alleles at the DRB1, DQA1, and DQB1 loci, were found to be strongly associated with T1D [14–18]. However, multiple non-HLA loci have also been reported to contribute to disease risk, including INS, CTLA4, PTPN22, IL2RA, IFIH1, CAPSLIL7R, CLEC16A, and PTPN2 [19]. In addition to genetics, other factors are thought to influence the rate and time of onset of disease in genetically predisposed individuals. Studies in twins have shown that, in some cases, concordance rate and timing of T1D development in monozygotic twins were incomplete and very different, respectively. Moreover, the rapid increase in T1D incidence over the past 60 years cannot be explained solely by genetics [3,20].

Epigenetic and environmental factors capable of altering the penetrance of major susceptibility genes or capable of increasing the

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penetrance of low-risk genes are currently thought to play a role in triggering autoimmunity and T1D development [21]. Components of an infant's diet (including cow's milk and gluten), increased maternal age, increased rate of postnatal growth, vitamin D deficiency, exposure to chemicals, and gut microbiota modifications have been associated with T1D [22–25]. However, most of the data regarding T1D triggering factors seem to indicate that viruses play a major role. Unfortunately, the data in the literature are heterogeneous and, in some cases, even contradictory [26–28]. A significant improvement in our knowledge of the relationships between viral infections and the development of T1D seems essential to improve the prevention of T1D in genetically susceptible individuals [29]. This paper discusses what is currently known about the role of viruses in T1D.

2. Evidence suggesting a potential correlation between viral infections and type 1 diabetes (T1D)

Most of the available data seem to indicate that viral infections play a role in favoring T1D development. Several studies have reported a seasonal pattern of T1D onset. In both the Northern and Southern hemispheres, more T1D cases are diagnosed during cold months [30–32]. Because viral infections are significantly more common in winter than in summer, this was considered indirect evidence of the role that viruses play in triggering T1D development. A similar conclusion was drawn from studies that evaluated potential relationships between the occurrence of viral respiratory tract infections in early life and the development of beta-cell damage even many years later. Rasmussen et al. reported that the estimated hazard ratio for islet autoimmunity in early infancy in genetically predisposed children was significantly higher when they had suffered from severe, probably viral, lower respiratory infections [33]. Moreover, Beyerlein et al. found that recurrent viral respiratory tract infections in the first semester of life were associated with islet autoimmunity and with the development of T1D at approximately 8 years of age [34,35]. A potential association between viruses and T1D is further suggested by the evidence that some viruses, particularly coxsackieviruses, can induce T1D in experimental animals and can be isolated from the pancreas of patients with recently onset disease [36–38]. However, the most relevant information comes from prospective studies that mainly focus on enteroviruses (EVs) and herpes viruses (HVs). After evidence that the incidence of diabetes was increased after EV epidemics [39], several studies to confirm or to exclude the role of EVs were carried out. Those published until May 2010 were systematically reviewed and analyzed by Yeung et al. [40]. Cohort or case-control studies using molecular methods to measure enterovirus RNA or viral protein in blood, stool, or tissue in a total of 1931 pre-diabetes and diabetes cases and 2517 controls patients were reviewed. They concluded that a strict association between EV infection and T1D could be demonstrated [40]. Evidence of infection was 10 times more common in children at the diagnosis of T1D compared with controls (odds ratio [OR]) 9.8, 95% confidence interval [CI] 5.5–17.4], and the OR of infection was also higher in children with pre-diabetes than in controls (OR 3.7, 95% CI 2.1–6.8). More recent prospective studies have significantly improved our knowledge of the possible role of EVs as a trigger of T1D. In MIDIA [41] and DAISY studies [42], EVs could be detected more frequently in the blood of patients at the stage of anti-islet autoimmunity activation than in the blood of healthy controls. Moreover, it was reported that EV infection preceded islet autoimmunity by more than a year, as evidenced by the more frequent detection of these viruses in the stools of children in whom islet autoantibodies were later detected, than in those from healthy individuals [43]. Finally, it was shown that the most common EVs to be potentially involved in islet damage were coxsackieviruses, and among these A2, A4, A16, B1, and B4 [44], and that not all of the EVs had the same potential, with some strains having no documented pathologic potential [45].

In addition to EVs, a second group of viruses has frequently been associated with T1D development: herpesviruses. Among them, Epstein-Barr virus (EBV) and cytomegalovirus (CMV)can under unusual conditions have a role in induction of T1D. EBV remains in infected individuals for years [46] and its reactivation or primary infection in patients with immunodeficiencies is associated with rare case of T1D [47]. The prevalence of antibody responses to EBV was found earlier and at significantly higher levels in patients suffering from T1D than in control subjects (OR 6.6; 95% CI 2.0–25.7), whereas no differences were found when the immune response to other viruses was tested [48].

Significantly more controversial are the reports regarding CMV. In addition to studies that found no evidence of the virus in pancreas samples or of an association between congenital CMV infection and later T1D development [49], there are studies that found evidence of a strict correlation between the presence of the CMV genome in the lymphocytes of patients and the detection of specific islet autoantibodies [50,51].

Other viruses that are potentially associated with T1D are parechoviruses, rotaviruses, influenza viruses, rubella and mumps virus. Antibodies against Ljingan virus, a member of the parechovirus family, have been detected in patients with insulin autoantibodies [52,53]. Experimental studies have demonstrated that rotavirus infection favors the apoptosis of pancreatic cells and may induce a reduction in insulin secretion [54]. Regarding influenza viruses, although previous studies have suggested a possible pathogenic role of these infectious agents [54,55], a recently performed study in which IgG class antibodies to influenza A virus were analyzed in children with permanent positivity for islet autoantibodies and in healthy controls with an HLA-conferred risk of T1D development found no association between influenza A infection and the development of islet autoimmunity [56]. Finally, although both rubella [57] and mumps [58,59] viruses have been associated with T1D, the evidence that the widespread use of the measles, mumps, and rubella vaccine has neither increased nor reduced the incidence of T1D seems to indicate that these viruses have poor relevance, if any, as trigger factors of T1D development [60].

Together with a negative role, viruses can have a positive effect by protecting genetically predisposed individuals from T1D development. This seems to agree with the so-called hygiene hypothesis, in which a reduction in infection may lead to an increase in several chronic disorders, including those caused by autoimmunity due to a failure in immune regulation involving various regulatory T cell subsets and Toll-like receptor stimulation. Infections, by contrast, tend to maintain normal immune responses, favoring microbial elimination [61]. The positive impact of viral infections on T1D onset has been evidenced in experimental animals, particularly in the NOD mouse. This animal presents several characteristics that are quite similar to those of genetically predisposed humans [62]. Tracy et al. reported that the inoculation of young NOD animals with coxsackievirus B3 was followed by long-term protection from T1D rather than by the development of the disease as was expected [63]. The same protective role was demonstrated by Dyrberg et al. when NOD mice were infected with lymphocytic choriomeningitis virus [64]. Finally, it was shown that the infection of this mouse with the murine gammaherpesvirus-68 [65] or with the reovirus strain type 3 Abney [66] reduces or delays the onset of T1D, although insulitis is not prevented.

3. How viruses might influence pancreatic beta-cell function

Various hypotheses have been made to explain the potential interactions between viruses and the host that might lead to T1D. One of the theories proposed to explain the induction of T1D considers a direct effect of viruses on beta-cell function that leads to cell death. Some viruses can infect beta-cells, and it was supposed that this might lead directly to severe damage of the pancreatic islets [38,67,68]. The sudden onset of severe T1D after viral infection has been demonstrated in several experimental animals [69]. Moreover, some rare cases of fulminant T1D in humans are associated with clinical and laboratory