Epidemiology and Risk Factors of Type 1 Diabetes

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Abstract

Type 1 diabetes (T1D) is one of the most widespread chronic diseases of childhood. T1D results from the autoimmune destruction of insulin-producing beta cells in the pancreas. Genetic, epigenetic, metabolic, and environmental factors act together to precipitate the onset of the disease. Clinical T1D represents the end stage of a process resulting from the progressive beta-cell destruction following an asymptomatic period that may last for years. This knowledge, together with recent advances in the ability to identify individuals at increased risk for clinical disease, has paved the way for trials aimed at preventing or delaying the clinical onset of T1D. Individuals at risk for T1D can be identified by a positive family history or by genetic, immunological, or metabolic markers. These markers can be combined to achieve a higher positive predictive value for T1D and to identify those individuals to be selected for intervention trials.

The purpose of this chapter is to set out the epidemiology and the main risk factors which characterizes T1D.

Keywords

Age · Body mass index (BMI) · Epidemiology · Geography · Gender · Risk factors · Seasonality · Type 1 diabetes

Introduction

Type 1 diabetes (T1D) is an heterogeneous disorder characterized by damage of pancreatic beta cells, terminating in absolute insulin deficiency. Genetic, metabolic, and environmental factors act together to precipitate the onset of the disease. The excess mortality associated with complications of T1D and the increasing incidence of childhood T1D emphasize the importance of therapeutic strategies to prevent this chronic metabolic disorder. T1D is one of the most widespread chronic diseases of childhood, affecting children, adolescents, and young adults (International Diabetes Federation (IDF)).

The global incidence of T1D in children and adolescents is rising with an estimated overall annual increase of approximately 3%. T1D accounts for about 10% of all cases of diabetes, occurs most commonly in people of European descent, and affects two million people in Europe and North America. The lowest incidence has been found in Asia and Oceania and the highest in Europe.

The increase in incidence of T1D has been shown in countries having both high- and low-prevalence figures (see Fig. 1), with an indication of a steeper increase in some of the low-prevalence countries. Several European studies have suggested that, in relative terms, the increase is more pronounced in young children. Although T1D usually accounts for only a minority of the total burden of diabetes in a population, it is the predominant form of the disease in younger age groups in most developed countries.

There are strong indications of geographic differences in trend, but the overall annual increase is estimated around 3%. About 79,100 children under 15 years are

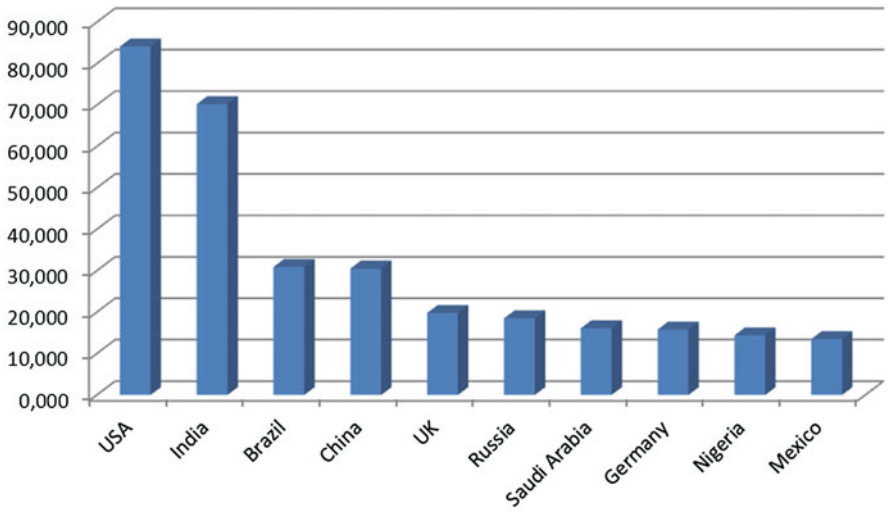


Fig. 1 Top 10 countries for number of children with type 1 diabetes (0–14 years) (Data from Diabetes ATLAS (International Diabetes Federation (IDF)))

estimated to develop T1D annually worldwide. Of the estimated 497,100 children living with T1D, 26% live in Europe Region and 22% in the North America and Caribbean Region (https://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf).

Increasingly efforts need to be directed toward early diagnosis of T1D because it is a condition leading to early complications and the potential availability of disease-modifying interventions underscores the need for early diagnosis.

Incidence of Type 1 Diabetes

The incidence of T1D differs based upon geography, ethnicity, age, gender, family history, and BMI. The incidence of T1D begins sharply to rise at about 9 months of age, continues to rise until age 12–14 years, and then declines (Tuomilehto 2013). A similar pattern is seen in many other countries irrespective of whether the overall incidence of T1D is low or high (Patterson et al. 2014).

Geographical Differences

The incidence of childhood T1D varies worldwide (You and Henneberg 2016; Beyerlein et al. 2015; Miller et al. 2011). In Europe and China, the risk appears to rise as the geographical latitude increases (Kalliora et al. 2011; Patterson et al. 2012), but this North-South disparity is not found in the United States, even after adjusting for racial and ethnic variation (Liese et al. 2010).

In Europe, the highest incidence rates are in Finland (Harjutsalo et al. 2013) and in Sardinia (Italy) (Fortunato et al. 2016).

Rates in these countries are almost 400 times that of Venezuela and parts of China, which have the lowest incidence (0.1–0.5 per 100,000 children) (Zhao et al. 2014). The incidence rate of T1D in the white population of the United States is higher than those recorded for countries of Northern Europe but significantly lower than those in Sweden and Finland. In the United States, the incidence of T1D in non-Hispanic white children and adolescents is 23.6 per 100,000 per year, and rates are substantially lower in other racial or ethnic groups (Bell et al. 2009).

Extensive dissimilarities in incidence occur between neighboring areas of similar latitude, suggesting the presence of other contributing risk factors and demonstrating the complexity of the pathogenesis of T1D and more interestingly the observation that when people relocate from a region of low to high incidence, their risk of developing T1D also increases, underlying a causative role for environmental factors.

Seasonality

Seasonal disparity at the time of diagnosis of T1D has been described from many records both in Europe (Moltchanova et al. 2009) and worldwide (Kalliora et al. 2011) with most reports suggesting a winter peak. Seasonal variation in sunshine hours is particularly relevant to vitamin D levels because most of the body's vitamin D is synthesized through the action of sunlight on the skin. The evidence from animal experiments and observational studies in humans of a role for vitamin D in the etiology of T1D has been widely described in literature, and some data suggest a role of vitamin D in the pathogenic process leading to the destruction of the insulin-producing cells (Sørensen et al. 2016; Altieri et al. 2016; Mäkinen et al. 2016).

Two meta-analyses of retrospective studies indicated that the risk of T1D was lower in infants who were supplemented with vitamin D (calcitriol) compared with those who were not supplemented (pooled odds ratio 0.71) (Miettinen et al. 2012; Zipitis and Akobeng 2008). On the other hand, the DAISY study examined 25-hydroxyvitamin D concentrations in infancy and throughout childhood and found no association with islet autoimmunity or progression to T1D (Simpson et al. 2011), and also two studies carried out in new-onset T1D reported no effect of vitamin D supplementation on sustained insulin production (Bizzarri et al. 2010; Walter et al. 2010).

In summary, despite continuing interest in vitamin D supplementation as a potential intervention to prevent islet autoimmunity and T1D, there is surprisingly little supporting evidence from prospective birth cohort studies (Rewers and Ludvigsson 2016).

Age

T1D is a heterogeneous disease, and it is the major type of diabetes in youth, accounting for $\geq$85% of all diabetes cases in youth $<$20 years of age worldwide (Kalliora et al. 2011; Chowdhury 2015). In general, the incidence rate increases from

birth and peaks between the ages of 10 and 14 years during puberty (Kalliora et al. 2011; Chowdhury 2015). Incidence rates decline after puberty and appear to stabilize in young adulthood (15–29 years).

A subgroup of individuals who develop diabetes in later life with clinical features of T2D but test positive for GAD autoantibodies are called LADA (latent autoimmune diabetes in the adults) (Leslie et al. 2006, 2008). The three criteria conventionally used to describe LADA are non-specific, namely, age at diagnosis, autoantibody positivity, and need for insulin treatment. Definitions of adult age range from 15 to 30 years, extending to all ages or up to 70 years. Up to 10% of adults initially thought to have T2D are found to have antibodies associated with T1D, and beta-cell destruction in adults appears to occur at a much slower rate than in young T1D cases, often delaying the need for insulin therapy after diagnosis.

The increasing incidence of T1D throughout the world is especially marked in young children (Patterson et al. 2009). The incidence of T1D in adults is lower than in children, although approximately one-fourth of persons with T1D are diagnosed as adults (Chiang et al. 2014; Lado and Lipman 2016).

Gender

Although most common autoimmune diseases disproportionately affect females, on average girls and boys are equally affected with T1D in young populations (Soltesz et al. 2007). A distinctive pattern has been observed such that regions with a high incidence of T1D (populations of European origin) have a male excess, whereas regions with a low incidence (populations of non-European origin) report a female excess (Svensson et al. 2003; Ostman et al. 2008). In contrast, clear male dominance has emerged from most studies of patients with T1D diagnosed between 15 and 40 years (Gale and Gillespie 2001; Kyvik et al. 2004). Adult T1D appears to differ from other common autoimmune diseases, which typically show a strong female excess, as does diabetes in the nonobese diabetic (NOD) mouse.

BMI

In 2001, Terry Wilkin (2001) presented the "accelerator hypothesis" in which he suggested that T1D and T2D could be defined the same disorder differentiated by the rate of beta-cell loss (Boitard et al. 2005). Since then literature has supported this hypothesis showing that BMI and changes in weight are inversely related to age at diagnosis for T1D. Knerr and colleagues in a large group of T1D children showed that a higher BMI is associated with a younger age at onset of T1D and that an increased weight gain could be considered a risk factor for early manifestation of the disease (Knerr et al. 2005). Moreover, Dabelea et al. (2006), in another study, concluded that an increasing BMI is associated with younger age at diagnosis only in subjects with a reduced beta-cell function and hypothesized that obesity may accelerate the onset of T1D.

Risk Factors for Type 1 Diabetes

Evidence for the role of environmental factors in the development of autoimmune diabetes is provided by population, migration, and twin studies. In North America and Europe, and possibly worldwide, population studies have shown that the incidence of childhood T1D has been increasing over the past 100 years, particularly in younger age groups (Pociot and Lernmark 2016). On the other hand, the proportion of diabetic patients with high diabetes-risk genotypes (DR4-DQ8/DR3-DQ2) has decreased and lower-risk genotypes (DR4-DQ8/X and DR3-DQ2/X) has increased, implying an increasing role in environmental factors (acting in genetically susceptible persons) in promoting diabetes (Rewers and Ludvigsson 2016). Migration studies have shown that Asian children in families who have moved to Britain show an increased incidence in T1D much higher than the incidence in their native countries and approaching that of the indigenous population (Bodansky et al. 1992). Although, it should be noted that in contrast to this, Sardinian migrants to Italy retained their ancestral high incidence of diabetes, suggesting genetics plays a stronger role in determining disease susceptibility (Muntoni et al. 1997). Twin studies have shown that if one of a monozygotic twin pair has diabetes, the risk of their nondiabetic co-twin of developing diabetes after 40 years is estimated to be 50% (Redondo et al. 2001). Interestingly, if the proband is diagnosed before the age of 25 years, the probability of the co-twin developing diabetes is 38%, compared with only 6% for twins of probands diagnosed later (Redondo et al. 2001; Hyttinen et al. 2003). This age of onset-dependent difference in the risk of a monozygotic co-twin developing diabetes cannot be explained by differences in HLA-type distribution (Redondo et al. 2001).

The primary risk factor for beta-cell autoimmunity is genetic, mainly occurring in individuals with either HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes or both, but a trigger from the environment is generally needed (Pociot and Lernmark 2016).

T1D pathogenesis can be divided into three stages, (1) appearance of beta-cell autoimmunity, normoglycemia and no symptoms; (2) beta-cell autoimmunity, dysglycemia and no symptoms; and (3) beta-cell autoimmunity, dysglycemia and symptoms of diabetes (Insel et al. 2015), and the genetic association with each one of the three stages can differ (Pociot and Lernmark 2016).

Portuesi R and colleagues assessed the risk conferred by HLA-DRB1, INS-VNTR, and PTPN22 single genes on the onset of T1D and the joint risk conferred by all these three susceptibility loci using the Bayesian network (BN) approach in a case-control French cohort, consisting of 868 T1D patients and 73 French control subjects, and in a French family data set consisting of 1694 T1D patients and 2340 controls. This is the first study based on both case-control and family data sets, showing the joint effect of HLA, INS, and PTPN22 in a T1D Caucasian population with a wide range of age at T1D onset (Portuesi et al. 2013) (see Fig. 2).

A number of investigations have been made into putative risk factors, other than strictly genetic effects, for the development of autoimmune diabetes, and the major suspects are described below (see Table 1):

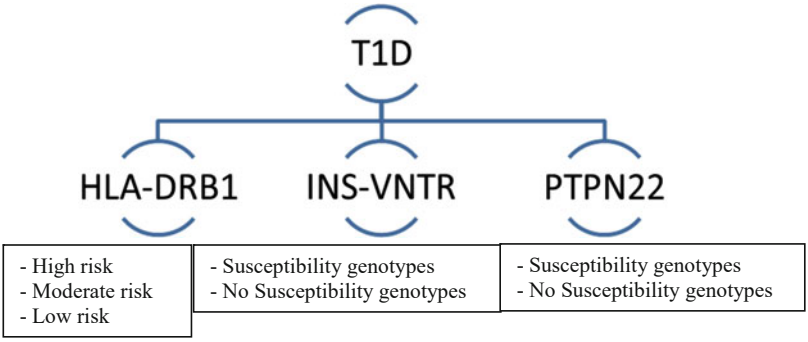
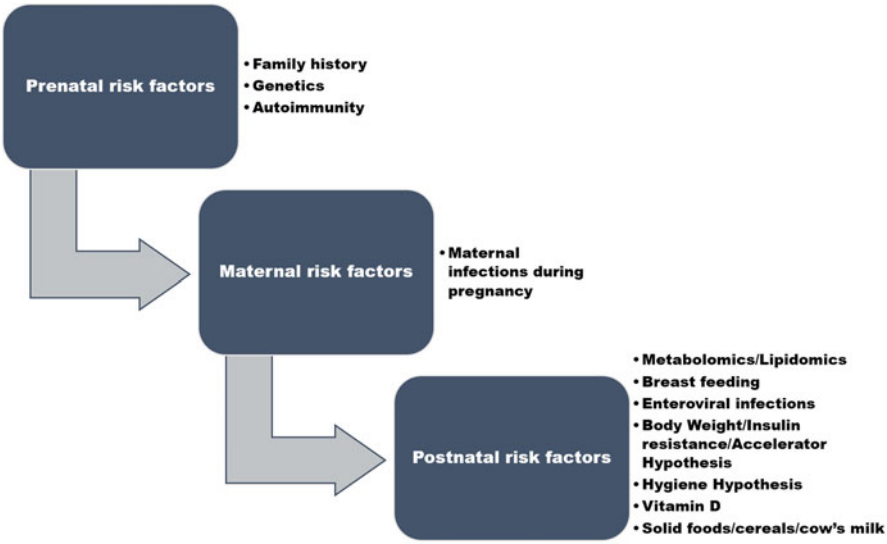


Fig. 2 The Bayesian network implemented to assess risk to develop T1D (Modified from Bodansky et al. (1992))

Table 1 Major risk factors for T1D



- *Family history.* According to a large Swedish study, a family history of diabetes (a first-degree relative diagnosed with diabetes) was associated with a four times increased risk in prevalence of LADA, which may be attributable to an inherited reduction in insulin secretion (Carlsson et al. 2007). Otherwise, the majority of studies into familial risk of autoimmune diabetes have considered only childhood-onset T1D. Siblings of diabetes subjects have a 15 times increased risk of developing diabetes compared to the general population (Insel et al. 2015). Interestingly, familial diabetes risk appears to be transmitted down the paternal line, with the proportion of affected children having a father with T1D exceeding

that of affected children having a mother with T1D (3.4% vs. 1.8%, respectively) (Bingley and Gale 2006). Also, there may be preferential transmission of disease from a father to his daughter than to his son (Gillespie et al. 2002).

- *Infections*. Several ecological reports and case report studies have drawn attention to viral infections as a potential cause of T1D. Bacterial infections are rarely discussed, although bacteria as a cause of pancreatic lesions cannot be excluded. Several viruses have been implicated, with enteroviruses having the strongest evidence from studies in animal models and also in human beings (Rewers and Ludvigsson 2016). Infection with an enterovirus, particularly the coxsackie B virus, has been the subject of a number of investigations looking at potential risk factors for T1D (Sane et al. 2013). Although the results have not always been consistent, a recent systematic review and meta-analysis of case-control studies have shown a strong association between enteroviral infection and T1D-related autoimmunity (odds ratio 3.7) and clinical T1D (odds ratio 9.8). The relationship is most prominent in subjects carrying high-risk HLA-DQB1 genotypes, representing a gene-environment interaction, which precipitates diabetes. Although the causal mechanism connecting enteroviral infection to T1D is not well understood, hypotheses include direct infection of beta cells causing functional impairment and cell lysis (Wen et al. 2008; Jaïdane et al. 2010) and molecular mimicry resulting in autoimmune destruction of beta cells (Stene et al. 2010). The seasonal variation in the first appearance of diabetes-associated antibodies, considered the earliest predictors of T1D and being higher during colder months, also provides some (weak) evidence for an association between viral infections in (also more frequent in winter) T1D. Finally, a fascinating line of evidence proposes that enteroviral infections during pregnancy might result in persistent infection and islet autoimmunity in the mother and offspring (Viskari et al. 2012).
- *Intestinal microbiota*. Some of the candidate environmental factors for T1D (cesarean delivery, early childhood diet, and use of antibiotics) are intertwined with the development and function of the human microbiome (Rewers and Ludvigsson 2016). Gut microbes influence lipid and glucose metabolism, as well as immunity and systemic inflammation outside of the intestine (Wen et al. 2008). Commensal microbiota might modulate the risk of T1D, but studies so far have been underpowered. Some have reported lower microbial diversity in children with islet autoimmunity before progression to diabetes, compared with healthy controls (Rewers and Ludvigsson 2016).
- *Solid food/cereals*. Dietary exposures in infancy have been implicated in the etiology of T1D, and there is evidence in literature that too early or too late introduction of solids might increase baby's risk for T1D. In the DAISY study, the timing of introduction of any type of cereal (gluten and non-gluten containing) was associated with an increased risk of islet autoimmunity with nadir at introduction at 4–6 months of life (Norris et al. 2003), while the BABYDIET study, a primary prevention trial, was designed to investigate whether delay of the introduction of dietary gluten can prevent the development of islet autoimmunity in newborns with a first-degree relative with T1D, who are at genetically high risk of

T1D 14; children who participate in BABYDIET were randomly assigned to one of two dietary intervention groups that introduced cereals that contain gluten either at age 6 months, but no benefit was found in delaying gluten exposure with respect to autoimmunity associated with diabetes or celiac disease (Hummel et al. 2011).

- *Cord blood/metabolomic/lipidomic*. Children developing T1D may have risk markers already in their umbilical cord blood. It is hypothesized that the risk for T1D at an early age may be increased by a pathogenic pregnancy and be reflected in altered cord blood composition. La Torre and colleagues (La Torre et al. 2013) identified a total of 106 lipid metabolites in the cord blood samples of the 152 children, including phospholipids (PLs) and triglycerides (TGs), and they were able to demonstrate that low levels of phosphatidylcholines and phosphatidylethanolamines increased the risk for T1D diagnosed before 4 years of age.
- *Hygiene hypothesis*. Decreasing infections in Europe in the last 50 years correlates with the trend for increasing autoimmune disease. A number of explanations have been proposed including infection-induced upregulation of Treg cells and the subsequent suppression of autoimmunity-promoting Th1 responses. The timing of the infection is also important, and appropriate "protective infections" may delay the onset of diabetes in susceptible populations (Jaïdane et al. 2010).
- *Body mass index (BMI)*. BMI can predict progression to T1D in children, particularly in the context of impaired beta-cell function (low fasting C-peptide) (Dabelea et al. 2006), and in this context, Barker and colleagues investigated whether BMI measured at diagnosis was an independent predictor of C-peptide decline 1-year post-diagnosis (Lauria et al. 2015). A multicentre longitudinal study was carried out at the time of T1D diagnosis and up to 1-year follow-up in more than 3000 subjects. In individuals diagnosed between 0 and 5 years and 5 and 10 years and those diagnosed >18 years, no association was found between BMI and C-peptide declines. In patients aged 10–18 years, higher BMI at baseline was associated with a greater decline in fasting C-peptide over 1 year with a decrease (β 95% CI; P value) of 0.025 (0.010, 0.041) nM/kg per m^2 higher baseline BMI ($P = 0.001$). This association remained significant after adjusting for gender and differences in HbA1c and insulin dose ($\beta = 0.026$, 95% CI = 0.0097, 0.042; $P = 0.002$). This study indicates that increased body weight and increased insulin demand are associated with more rapid disease progression after diagnosis of T1D in an age group 10–18 years (Lauria et al. 2015).
- *Early weight gain*. Weight gain in the first 2 years of life, particularly in the context of HLA-susceptible persons, is associated with increased ICA in first-degree relatives (as children) of T1D patients; relatives of adult-onset diabetes cases have not been studied (Couper et al. 2009).
- *Insulin resistance*. In subjects with ICA, insulin resistance can predict those that are likely to progress to diabetes (Fourlanos et al. 2004). Insulin resistance could be accelerating the development of clinically overt diabetes or could be secondary to the systemic changes which occur in autoimmune disease, i.e., release of insulin resistance-promoting cytokines such as TNFα (Meah et al. 2016).

- *Breast-feeding*. Duration of breast-feeding, particularly short-term exclusive breast-feeding, particularly in the context of HLA-associated diabetes susceptibility genotypes has been found to be associated with childhood-onset type 1 diabetes (Nucci et al. 2015), although this has not been a consistent finding in similar investigations (Ziegler et al. 2003; Virtanen et al. 2006; Norris et al. 2003).
- *Cow's milk*. Most prospective birth cohort studies have not shown any link between early exposure to cows' milk and either islet autoimmunity or T1D. A large worldwide trial called TRIGR aimed to answer the question of whether cow's milk administered in early life is diabetogenic and whether the use of cow's milk hydrolysate can protect from the disease. The rationale behind the use of cow's milk hydrolysate for primary prevention of T1D is based on several epidemiological and in vitro studies indicating that intact cow's milk, if given before 3 months of age, may induce an immune response toward beta cells (Pozzilli et al. 2003). TRIGR is a double-blind randomized clinical trial of 2159 infants with HLA-conferred disease susceptibility and a first-degree relative with T1D recruited from May 2002 to January 2007 in 78 study centers in 15 countries; 1078 were randomized to be weaned to the extensively hydrolyzed casein formula, and 1081 were randomized to be weaned to a conventional cows' milk-based formula (TRIGR Study Group 2007; Knip et al. 2014). Primary outcome was positivity for at least two diabetes-associated autoantibodies out of four analyzed. Autoantibodies to insulin, glutamic acid decarboxylase, and the insulin-associated-2 (IA-2) molecule were analyzed using radiobinding assays and islet cell antibodies with immunofluorescence during a median observation period of 7.0 years (mean, 6.3 years). The absolute risk of positivity for two or more islet autoantibodies was 13.4% among those randomized to the casein hydrolysate formula ($n = 139$) versus 11.4% among those randomized to the conventional formula ($n = 117$). The unadjusted hazard ratio for positivity for two or more autoantibodies among those randomized to be weaned to the casein hydrolysate was 1.21 (95% CI, 0.94–1.54), compared with those randomized to the conventional formula, while the hazard ratio adjusted for HLA risk, duration of breast-feeding, vitamin D use, study formula duration and consumption, and region was 1.23 (95% CI, 0.96–1.58). In conclusion, TRIGR study showed that among infants at risk for T1D, the use of a hydrolyzed formula compared with a conventional formula did not reduce the incidence of diabetes-associated autoantibodies (Knip et al. 2014). The results of the effect of this treatment on diabetes insurgence are expected in 2017.
- *Age of introduction of complex nutrients*. Early introduction of gluten (e.g., via cow's milk) into an infant's diet has been shown to increase the risk of developing diabetes. A pilot intervention trial in which infants with risk-associated HLA-DQB1 haplotypes were given either conventional cow's milk or casein hydrolysate demonstrated decreased frequency of seroconversion to ICA in the casein hydrolysate arm (Akerblom et al. 2005), although a larger study will be needed to confirm the results.
- *Vitamin D*. Dietary vitamin D may be protective against T1D. Vitamin D levels may affect the immune response through the modulation of relative pro- and anti-inflammatory cytokine levels (Fronczak et al. 2003).

- *The overload hypothesis*. A number of environmental factors – in particular child growth and weight and fetal priming (where overfeeding or starving the fetus may alter metabolic programming, tending toward increased insulin resistance or increased liability to beta-cell death) – increase beta-cell stress on a background of autoimmunity, which could explain the tendency toward earlier development of T1D in European populations (Dahlquist 2006).
- *The accelerator hypothesis*. Previous reports have predicted greater risk of T1D among people who were heavier as young children. The accelerator hypothesis predicts earlier onset in heavier people. The relationships between fatness and age at diagnosis were examined in context of birth weight, weight change since birth, weight at diagnosis, BMI at diagnosis, and BMI 12 months later in 94 children aged 1–16 years presenting for management of acute-onset T1D by Kibirige and colleagues (2003), and the results of the study were consistent with the hypothesis that the age at presentation of T1D is associated with fatness.

Summary

T1D is one of the most common chronic diseases of childhood, and it accounts for approximately two-thirds of all cases of diabetes in patients younger than 18 years of age. T1D incidence varies up to 100-fold among different countries, and the incidence increases with the age of the children/adolescents.

Research on risk factors for T1D is an active area of research that will help to classify more precisely genetic and environmental triggers that could theoretically be targeted for intervention. While significant advances have been made in the clinical care of T1D with resultant improvements in quality of life and clinical outcomes, much more needs to be done to improve care of and ultimately to find a cure for T1D (Gale 2002).

Future research should focus on knowing environmental and genetic risk factors of T1D and its complications, preventive strategies, and causal treatment options. The prevalence, which doubled worldwide over the last decades, will increase further, and T1D will shift more and more into the focus of general practitioners. It becomes conclusive that T1D will be a burden for more and more patients and for the majority of health-care systems.

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