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## Chapter 1: Epidemiology of Type 1 Diabetes

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### Synopsis

This chapter describes the epidemiology of type 1 diabetes mellitus (T1D) around the world and across the lifespan. Epidemiologic patterns of T1D by demographic, geographic, biologic, cultural and other factors in populations are presented to gain insight about the etiology, natural history, risks, and complications of T1D. Data from large epidemiologic studies worldwide indicate that the incidence of T1D has been increasing by 2–5% worldwide and that the prevalence of T1D is approximately 1 in 300 in the US by 18 years of age. Research on risk factors for T1D is an active area of research to identify genetic and environmental triggers that could potentially 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 find a cure for T1D. Epidemiologic studies have an important on-going role to investigate the complex causes, clinical care, prevention, and cure of T1D.

### Keywords

type 1 diabetes; epidemiology; incidence; prevalence; children

### Introduction

This chapter describes the epidemiology of type 1 diabetes mellitus (T1D) around the world and across the lifespan. Epidemiologic patterns of T1D by demographic, geographic,

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biologic, cultural and other factors in populations are presented to gain insight about the etiology, natural history, risks, and complications of T1D. Studies of the epidemiology of T1D in diverse populations are aimed at the identification of causal factors of the disease and its complications. The elucidation of the complex interaction between genetic and environmental factors leading to T1D should inform ongoing efforts to treat, prevent, and eventually cure T1D.

T1D is a heterogeneous disorder characterized by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. The majority of cases are attributable to an autoimmune-mediated destruction of beta cells (type 1a) while a small minority of cases results from an idiopathic destruction or failure of beta cells (type 1b). T1D accounts for 5–10% of the total cases of diabetes worldwide<sup>1</sup>. A second and more prevalent category, type 2 diabetes (T2D), is characterized by a combination of resistance to insulin action and inadequate compensatory insulin secretory response<sup>1</sup>. T1D has been historically, and continues to be, the most common type of diabetes in children and adolescents, although type 2 diabetes (T2D) is increasingly diagnosed in youth<sup>2,3</sup>.

In this chapter, we will review the epidemiology of T1D in the following order: Incidence and Prevalence, Risk Factors, Clinical Course, Treatment and Management, and Complications. Other reviews of the Epidemiology of T1D have been published recently<sup>4</sup> including a text on the epidemiology of diabetes in youth<sup>5</sup>. Additionally, some topics in this chapter will be reviewed in greater detail in later sections and we provide these references for the reader.

## Incidence and Prevalence of T1D

The current prevailing paradigm on the etiology of T1D hypothesizes that environmentally triggered autoimmune destruction of pancreatic beta cells occurs against the background of genetic risk<sup>6</sup>, although alternate hypotheses exist<sup>7,8</sup>. As such, it follows that global variation in the incidence, prevalence, and temporal trends in T1D are reported. In this section, findings from large T1D registry studies such as the World Health Organization Multinational Project for Childhood Diabetes, known as the DIAMOND Project<sup>9,10</sup>, EURODIAB<sup>11,12</sup>, and the SEARCH for Diabetes in Youth (SEARCH) study will be emphasized<sup>2,3</sup>. Reports on trends in T1D are more commonly available from countries with better established public health surveillance systems and diabetes research infrastructure. As such, data that will allow for the study of T1D from the more developing world are a research priority.

The DIAMOND project was initiated by the World Health Organization in 1990 to address the public health implications of T1D with a main objective to describe the incidence of T1D in children. An initial report in 2000 described the incidence of T1D in children  $\leq 14$  years of age in 50 countries worldwide totaling 19,164 cases from a population of 75.1 million children (an estimated 4.5% of the world's population in this age range) from 1990–1994<sup>9</sup>. A greater than 350-fold difference in the incidence of T1D among the 100 populations worldwide was reported with age-adjusted incidences ranging from a low of 0.1/100,000 per year in China and Venezuela to a high of 36.5/100,000 in Finland and 36.8/100,000 per year in Sardinia. The lowest incidence ( $< 1/100,000$  per year) was reported in the populations from China and South America and the highest incidence ( $> 20/100,000$  per year) was reported in Sardinia, Finland, Sweden, Norway, Portugal, the UK, Canada, and New Zealand. The US populations included in the DIAMOND study were drawn from the states of Pennsylvania, Alabama, and Illinois reported incidences of 10–20/100,000 per year. Approximately half of the European populations reported incidence between 5–10/100,000 per year with the remainder having higher rates. The incidence of T1D increased

with age in most populations with the highest incidence observed in the 10–14 year olds. Within country variation was also reported with rates 3–5 times higher in Sardinia than in continental Italy, with similar variation reported within Portugal, New Zealand, and China. A statistically significant male-to-female excess in incidence was reported in 3 centers, but no populations reported a female excess. These authors hypothesize that the explanation for the variation within ethnic groups may be due to differences in genetic admixture or environmental/behavioral factors. They also reported that in countries undergoing rapid social change, population exposure to putative etiologic factors for T1D may change rapidly, highlighting the importance of such registries for the development and testing of genetic and environmental hypotheses on the pathogenesis of T1D.

In the United States, the SEARCH for Diabetes in Youth study has been designed to identify incident and prevalent cases of diabetes among individuals <20 years of age in a multi-center study design with a goal of estimating the incidence and prevalence of diabetes in the US by age, sex, and race/ethnicity<sup>3</sup>. In 2002–03, 1,905 youth with T1D were diagnosed in SEARCH from a population of more than 10 million person-years under surveillance. Rates were highest in non-Hispanic white youth as compared to other race/ethnicities and were slightly higher in females as compared to males (RR, 1.028; 95% CI, 1.025–1.030). The incidence rate of T1D in 2002–03 peaked in the age groups 5–9 years and 10–14 years and incidence per 100,000 person years by age group were as follows: 0–4 years, 14.3; 5–9 years, 22.1; 10–14 years 25.9; 15–19 years, 13.1. Dabelea notes that the T1D incidence rates from the SEARCH study are higher than previous US reports from Allegheny County<sup>13</sup>, and from Philadelphia<sup>14</sup> for non-Hispanic white children but lower than for African American children<sup>14</sup>; while the SEARCH rates for Hispanic youth are similar to those reported for Puerto Rican children in Philadelphia<sup>14,15</sup> but higher than that reported in Colorado in the 1980s<sup>16</sup>. For non-Hispanic whites, the incidence rate of T1D in SEARCH was >20/100,000 person years as compared to 16.5/100,000 in Allegheny County in the early 1990s. However, ascertainment techniques differ by study and must be considered when comparing incidence rates by study.

In the SEARCH study, the prevalence of T1D was 2.28/1000 in youth less than age 20 years or 5,399 cases in a population of ~3.5 million<sup>2</sup>. Among children <10 years of age, T1D accounted for almost all of the reported cases of diabetes, whereas in youth ages 10–19 years, the proportion with T2D out of the total sample of youth with diabetes ranged from 6% (in non-Hispanic whites) to 76% (in American Indians). The authors estimate that 154,369 youth in the US had diabetes (T1D, T2D or unspecified forms) in 2001.

### **Incidence: Temporal Trends**

An updated report from the DIAMOND project examined the trends in incidence of T1D from 1990–1999 in 114 populations from 57 countries. Based on 43,013 cases of T1D from a study population of 84 million children ≤14 years<sup>10</sup>, the average annual increase in incidence over this time period was 2.8% (95% CI 2.4–3.2%) with a slightly higher rate in the period 1995–1999, 3.4% (95% CI 2.7–4.3%), than in the period 1990–1994, 2.4% (95% CI 1.3–3.4%). These trends for increased incidence of T1D were seen across the world in the populations studied (4.0% in Asia, 3.2% in Europe, and 5.3% in North America) with the exception of Central American and the West Indies, where T1D is less prevalent, and where the trend was a decrease of 3.6%. Such reported increases cannot be attributed to genetic shifts in such a short period of time and the authors state that causative agents should be investigated in the environment or the gene-environment interaction. Furthermore, they note recent studies<sup>17–19</sup> demonstrate environmental factors have a stronger effect on individuals with lower risk genotypes as compared to those at higher risk genetically.

Using U.S. data from the Colorado IDDM study registry and the SEARCH study, the incidence of T1D was shown to increase over the past 3 decades<sup>20</sup>. The incidence of T1D was 14.8/100,000 per year (95% CI 14.0–15.6) in 1978–88 and was 23.9/100,000 per year (95% CI 22.2–25.6) in 2002–04 for the state of Colorado. During this 26 year period, the incidence of T1D increased by 2.3% (95% CI 1.6–3.1) per year with significant increases for both non-Hispanic white and Hispanic youth.

The EURODIAB ACE study group ascertained 16,362 cases of T1D in 44 centers throughout Europe and Israel covering a population of ~28 million children during the period 1989–94<sup>11</sup>. As in the DIAMOND report, the standardized annual incidence rate varied greatly from 3.2/100,000 person years in Macedonia to 40.2/100,000 person years in two regions of Finland. In this time period, the annual increase in the incidence rate of T1D was 3.4% (95% CI 2.5–4.4%) although the rate of increase was noted to be higher in some central European countries. The rates of increase were found to be the highest in the youngest age group: ages 0–4 years (6.3%, 95% CI 1.5–8.5%), 5–9 years (3.1%, 95% CI 1.5–4.8%), and 10–14 years (2.4%, 95% CI 1.0–3.8%), with earlier onset implying a longer burden of disease as well as the more immediate challenge of caring for T1D in a toddler.

## Risk Factors for Development of T1D

Various risk factors for development of T1D such as age, sex, race, genotype, geographic location, and seasonality will be reviewed in this section.

### Age

T1D is the major type of diabetes in youth, accounting for  $\geq 85\%$  of all diabetes cases in youth < 20 years of age worldwide<sup>2,21,22</sup>. In general, the incidence rate increases from birth and peaks between the ages of 10–14 years during puberty<sup>3,10,11</sup>. The increasing incidence of T1D throughout the world is especially marked in young children<sup>10,23</sup>. Registries in Europe suggest that recent incident rates of T1D were highest in the youngest age-group (0–4 years)<sup>11</sup>. Incidence rates decline after puberty and appear to stabilize in young adulthood (15–29 years). The incidence of T1D in adults is lower than in children, although approximately one fourth of persons with T1D are diagnosed as adults<sup>24</sup>. Clinical presentation occurs at all ages and as late as the 9th decade of life<sup>22</sup>. Up to 10% of adults initially thought to have type 2 diabetes are found to have antibodies associated with T1D<sup>25</sup> 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. Individuals diagnosed with autoimmune diabetes when they are adults have been referred to as having latent autoimmune diabetes of adults<sup>26,27</sup>.

### Gender

Although most common autoimmune diseases disproportionately affect females, on average girls and boys are equally affected with T1D in young populations<sup>28</sup>. 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<sup>29,30</sup>. Many reports indicate an excess of T1D cases in male adults after the pubertal years (male-female ratio  $\geq 1.5$ ) in populations of European origin<sup>31–34</sup>.

### Race/ethnicity

Worldwide differences in T1D by race/ethnicity are in part discussed earlier in this chapter where worldwide incidence rates and prevalence estimates are presented. In many of these reports, data are presented by comparisons within and between country or region, but not by

race/ethnicity per se, in part due to the fact that many of the countries either are relatively homogenous in regards to race/ethnicity or lack the power based on their sample size to examine rates by race/ethnicity. However, the SEARCH study does provide specific data on the role of race/ethnicity within the US<sup>35</sup>.

The SEARCH for Diabetes in Youth Study recently published a set of papers in a supplement to *Diabetes Care*<sup>35</sup> in which race and ethnic specific issues in diabetes in 9,174 American youth are reviewed for five major race and ethnic groups in the U.S., non-Hispanic white<sup>36</sup>, African American<sup>37</sup>, Hispanic<sup>38</sup>, Asian and Pacific Islander<sup>39</sup>, and Navajo<sup>40</sup> populations. In these papers, the authors estimate the prevalence and incidence of diabetes in youth <20 years by age, sex, race/ethnicity and diabetes type as well as characterize key risk factors for diabetic complications by race/ethnicity and diabetes type (see Table 1 for Incidence/Prevalence data in the SEARCH study by age and race-ethnicity).

In the non-Hispanic white population the prevalence of T1D was 2.0/1,000 and the incidence was 23.6/100,000 (with a slightly higher incidence rate for males than females [24.5 v 22.7 per 100,000, respectively, p=0.04]). The authors conclude that these rates of T1D among non-Hispanic white youth are among the highest in the world. These youth had adverse cardiometabolic risk profiles (>40% with elevated LDL, <3% met dietary recommendations for saturated fat, and among those ≥15 years of age 18% were current smokers) which put them at risk for future health complications related to diabetes.

In African American youth in the SEARCH study, the prevalence of T1D was 0.57/1,000 (95% CI 0.47– 0.69) for youth age 0–9 years and 2.04/1,000 (1.85–2.26) for youth 10–19 years. The incidence of T1D for 0–9 year olds and 10–19 year olds during 2002–05 was 15.7/100,000. Of the African American youth that attended the research visit with T1D, 50% of those ≥15 years had A1c ≥9.5% and 44.7% were either overweight or obese.

The incidence of T1D in Hispanic youth in the SEARCH study was 15.0/100,000 and 16.2/100,000 for females and males 0–14 years of age. Poor glycemic control as well as high LDL-cholesterol and triglycerides were common and 44% of these youth with T1D were overweight or obese.

The incidence of T1D among Asian and Pacific Islander youth was 6.4 and 7.4/100,000 person years in 0–9 and 10–19 years olds, respectively. The Pacific Islanders were more likely to be obese as compared to the Asian or Asian-Pacific Islanders (mean BMI 26 v 20 kg/m<sup>2</sup>, p<0.0001).

The majority of Navajo youth that were identified as having diabetes were diagnosed with T2D (66/83 in the SEARCH paper). The authors state that T1D is present in Navajos, but that it is infrequent and estimate that the prevalence of T1D in Navajo youth is <0.5/1,000 and the incidence <5/100,000 per year. Regardless of type, Navajo youth were likely to have poor glycemic control and a high prevalence of unhealthy behaviors and depressed mood.

## Genotype

Of the multiple genes implicated in susceptibility (and resistance) to T1D, the most important are the human leukocyte antigen (HLA) complex on chromosome 6, in particular the HLA class II. Two susceptibility haplotypes in the HLA class II region are now considered the principal susceptibility markers for T1D<sup>41</sup>. Although 90–95% of young children with T1D carry either or both susceptibility haplotypes, approximately 5% or fewer persons with HLA-conferred genetic susceptibility actually develop clinical disease<sup>42</sup>.



Approximately 40–50% familial clustering in T1D is attributable to allelic variation in the HLA region<sup>43</sup>. The remaining genetic risk is made up of many diverse genes, each having a small individual impact on genetic susceptibility<sup>41</sup>. A number of reports suggest a recent temporal trend of fewer high-risk HLA genotypes in youth diagnosed with T1D, suggesting an increased influence of environmental factors in the development of T1D during the past few decades<sup>19,44,45</sup>.

Although the majority of T1D cases occur in individuals without a family history of the disease, T1D is strongly influenced by genetic factors. In the United States, individuals with a first-degree relative with T1D have a 1 in 20 lifetime risk of developing T1D, compared to a 1 in 300 lifetime risk for the general population<sup>46</sup>. Monozygotic twins have a concordance rate of > 60% if followed long enough<sup>47</sup> whereas dizygotic twins have a concordance rate of 6% to 10%. Genetic susceptibility for T1D ranges from marked in childhood-onset T1D to a more modest effect in adult-onset T1D, with children having a higher identical twin concordance rate and a greater frequency of HLA genetic susceptibility<sup>48,49</sup>. Siblings of children with onset of T1D before the age of 5 years have a three- to five-fold greater cumulative risk of diabetes by age 20 compared to siblings of children diagnosed between 5 and 15 years of age<sup>50</sup>. Diabetes with onset before age 5 years is a marker of high familial risk and suggests a major role for genetic factors. The offspring of affected mothers have a 2% to 3% risk, whereas offspring of affected fathers have a 7% risk<sup>51</sup>.

An association between T1D and other autoimmune diseases, such as autoimmune thyroid disease, Addison's disease, celiac disease, and autoimmune gastritis, is well established<sup>52</sup>. The clustering of these autoimmune diseases is related to genes within the major histocompatibility complex<sup>53</sup>.

### Seasonality of onset and birth

Patterns in the seasonality for both the month of birth and the month of diagnosis of T1D have been reported. While the seasonality of T1D diagnosis seems intuitively obvious given the well-documented environmental role in T1D's pathogenesis, it is also hypothesized that the seasonal environment at birth may have an influence on diabetes incidence later in life. Among 9,737 youth with T1D in the SEARCH study, the percentage of observed to expected births differed across the months with a deficit of November-February births and an excess in April-July births. This birth month effect was not observed in youth recruited from the centers in the more southern locations (South Carolina, Hawaii, Southern California), but only in the more northern latitudes (Colorado, Washington, and Ohio)<sup>54</sup>. A report from Ukraine also reported a strong seasonal birth pattern with the lowest rates of T1D in December and the highest in April<sup>55</sup>. Similar reports of higher rates of T1D among youth born in Spring and lower rates among youth born in the Fall have been published from Europe<sup>55-58</sup>, New Zealand<sup>59</sup>, and Israel<sup>60</sup>, but not in other studies from Europe, East Asia or Cuba<sup>58,61-63</sup>.

One hypothesis to explain such seasonal variation in T1D by birth month is that of seasonal variation in maternal vitamin D levels and vitamin D's effect in both beta cells and immune cells. Vitamin D deficiency has been associated with T1D<sup>64,65</sup> and the use of cod liver oil (a rich source of vitamin D) during pregnancy<sup>66</sup> and the first year of life<sup>67</sup> has been associated with a lower risk of T1D. Recent reports suggest that vitamin D deficiency is common in the pediatric population in the US<sup>68</sup>, even in solar rich environments<sup>69</sup>.

A seasonal pattern in the onset of T1D with increased cases during late autumn, winter, and early spring has been well known and repeatedly confirmed in youth<sup>70</sup>. The seasonal variation in infections implicated to precipitate T1D is suspected to play a primary role in this observation. Reports on the seasonality of T1D in adults have been mixed, but a recent

report from Sweden on more than 5800 patients 15–34 years of age found the higher incidence during January–March and the lowest during May–July with no difference by gender<sup>70</sup>. Although viral disease has long been proposed as a potential trigger of beta cell destruction, insufficient exposure to early infections might increase the risk of T1D as the maturation of immune regulation after birth is driven by exposure to microbes<sup>71</sup>. The evidence linking specific infections with T1D remains inconclusive<sup>72</sup>.

### Other risk factors

Epidemiological studies have identified that environmental factors operating early in life appear to trigger the immune-mediated process in genetically susceptible individuals. That nongenetic factors play a role in the development of T1D is evidenced by migration studies, rising incidence within genetically stable populations, and twin studies. The environmental triggers which initiate pancreatic beta cell destruction remain largely unknown.

Nutritional factors that have been investigated include cow's milk, breastfeeding, wheat gluten, and vitamins D and E<sup>42</sup>. Evidence regarding early introduction of cow's milk (or protective effects of breast milk consumption) in infants contributing to the development of childhood T1D is equivocal<sup>73–76</sup> and may depend on genetic susceptibility<sup>77</sup>. Timing of introduction of cereals/gluten or other foods to the infant diet has been suggested to alter risk for autoimmunity and development of T1D<sup>78–80</sup>. Increased use of vitamin D supplementation during infancy has been associated with reduced risk for childhood T1D<sup>81</sup>. Increased maternal consumption of vitamin D during pregnancy has also been associated with decreased risk of islet autoimmunity in the offspring<sup>82</sup>. A protective association was observed for serum alpha tocopherol in relation to T1D<sup>83</sup>. Despite these intriguing associations, there is little firm evidence of the significance of nutritional factors in the etiology of T1D.

### Clinical course

The clinical course of T1D is typically characterized by the acute onset of the classic symptoms of diabetes: polyuria, polydipsia, and weight loss. However, given the increased awareness of T1D as well as research studies in which at-risk children are screened for diabetes autoantibodies, some youth present with sufficient residual beta cell function to be maintained on low doses of insulin, often once daily, at the time of diagnosis. The course of autoimmune diabetes is characterized by on-going beta cell destruction and increased need for exogenous insulin. Identification of patients at risk for T1D and interventions to slow or halt autoimmune beta cell destruction are the focus of intense investigation (see Bonifacio and Ziegler). This general period with residual beta cell function and insulin secretion is referred to as the 'honeymoon' period during which management of glycemia is greatly aided by residual autonomous insulin production. As residual beta cell function diminishes, as evidenced by unmeasurable levels of c-peptide in serum, the management of T1D becomes increasingly complex and challenging for the children, their parents, and health care professionals.

As the clinical onset of T1D follows an acute course in most cases, an important issue at the presentation of T1D is that of the symptoms and severity of T1D, in particular that of diabetic ketoacidosis (DKA). The EURODIAB group reported on the frequency, severity, and geographical variation of DKA at presentation of T1D across 24 centers in Europe that included 1260 children at diagnosis of T1D<sup>12</sup>. Polyuria was the most common presenting symptom (96%), followed by weight loss (61%) and fatigue (52%). Duration of symptoms was less than 2 weeks in only 25% of the children, although this was more common in children <5 years of age, suggesting that efforts to educate populations on T1D's classic symptoms could improve early diagnosis and reduce the severity of metabolic derangement

at presentation. DKA, defined as  $\text{pH} < 7.3$ , was reported in 42% of children, with 33% having  $\text{pH}$  between 7.3 and 7.1 and 9% with severe DKA ( $< 7.1$ ). A strong inverse correlation between the background rate of T1D and proportion of newly diagnosed youth presenting with DKA was reported such that in centers with more T1D children were more likely to be diagnosed with T1D prior to the development of this metabolic emergency.

## Treatment and management

A number of therapeutic options for persons with T1D currently exist which include multiple daily injections of rapid acting insulin with meals combined with a daily basal insulin as well as continuous subcutaneous insulin infusion via an insulin pump. Other regimens such as pre-mixed insulin are also used in certain clinical situations. Guidelines for the care of T1D in children<sup>84</sup> and adults<sup>85</sup> have been published. Additionally, screening recommendations exist to monitor for the microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular) complications of T1D (Melendez-Ramirez, Richards, and Cefalu).

Glycemic control is the cornerstone of diabetes care. However, even in the Diabetes Control and Complications Trial (DCCT) the mean A1c for adolescents as compared to adults was 1–2% higher in both the intensive and conventionally treated arms. Despite this, rates of hypoglycemia were higher in adolescents than in adults<sup>86</sup>. More recently, studies published post-DCCT have shown that mean levels of A1c have remained higher than current glycemic goals with the Hvidore study reporting a mean A1c of 8.6% in over 2,000 youth with T1D worldwide<sup>87</sup>. Similarly, data from the SEARCH study reports a mean A1c of 8.2% in youth with T1D with 17% having an A1c  $\geq 9.5\%$ <sup>88</sup>. Of note, these data from Hvidore and SEARCH are post-DCCT in which it has been shown conclusively that intensive glycemic control improves vascular outcomes in T1D. A number of factors have been suggested to play a role in poorer glycemic control in youth than in adults including: insulin resistance of puberty, fear of hypoglycemia (especially in youth with hypoglycemic unawareness and the inability to effectively communicate to care-givers about this), and the psychological challenges of adolescence, among others<sup>89</sup>. In the SEARCH study, the statistically significant correlates of poorer glycemic control in the multivariate model for T1D were younger age, longer diabetes duration, weight  $< 85$ th percentile (vs being obese), living in a single parent household or other household structure (vs living in a 2-parent household), type of diabetes care provider (adult endocrinologist or none vs pediatric endocrinologist), race/ethnicity other than non-Hispanic white, being female, and lower parental education<sup>88</sup>.

Insulin pump (continuous subcutaneous insulin infusion [CSII]) therapy became more widely accepted for youth with T1D in the mid-1990's after the availability of rapid-acting insulin. Previously, pediatric diabetologists were cautious about pump use in children, particularly as a result of the three-fold increase in severe hypoglycemia reported amongst intensively treated patients in DCCT<sup>90</sup>. Of those in the DCCT, 2/3 used an insulin pump at some time and all used regular insulin in their pumps. With advances in insulin development and in pump features, however, the fear of severe hypoglycemia associated with intensive diabetes management has diminished. Numerous reviews of insulin pump therapy exist<sup>91–93</sup>.

In the SEARCH study, sociodemographic characteristics were associated with insulin regimen. Insulin pump therapy was more frequently used by older youth, females, non-Hispanic whites, and families with higher income and education ( $P = .02$  for females,  $P < .001$  for others). Insulin pump use was associated with the lowest hemoglobin A1C levels in all age groups<sup>94</sup>.



There is great hope that technological advances will lead to improved glycemic outcomes. One such advance, the development of continuous glucose monitors (CGM) was evaluated in a recent Juvenile Diabetes Research Foundation (JDRF) funded clinical trial. Among children and adults with T1D with a A1c  $\geq 7.0\%$  at enrollment in the study, a significant reduction in A1c was observed in adults ( $\geq 25$  years) but not in participants 5–14 years or 15–24 years when subjects assigned to the CGM use were compared to the controls<sup>95</sup>. However, when further stratified by CGM use, reductions in A1c were observed among children and young adults who wore the CGM for at least 6 days a week during the study period<sup>96</sup>. Among study participants whose A1c was  $<7.0\%$  at enrollment in the trial, of which about half were  $< 25$  years of age, the CGM group was able to maintain A1c levels at baseline values with less biochemical hypoglycemia, whereas A1c levels rose over time in the control group<sup>97</sup>. Further research is needed to identify barriers and address challenges to improved care in youth with T1D.

## Prevalence of complications

The DCCT demonstrated that intensive glycemic control reduces the long-term vascular complications of hyperglycemia in T1D. Unfortunately, diabetic complications continue to be a major cause of morbidity and mortality in persons with T1D and cardiovascular disease (CVD) is the leading cause of death<sup>98</sup>. Moreover, intensively controlled blood glucose often comes at the cost of increased hypoglycemia compared to less intensive (or pre-DCCT conventional) management<sup>99,100</sup>. Specifically, improved glycemic control in the DCCT was associated with a 2–6 fold increase in severe hypoglycemia in intensive as compared to conventionally treated subjects<sup>101</sup>.

However, in the past few decades a number of advances have been made in the care of persons with T1D which include home glucose monitoring<sup>102</sup>, development of insulin analogues<sup>103</sup>, demonstration of the benefit of intensive diabetes management on the prevention of microvascular<sup>86,99</sup> and macrovascular disease<sup>104,105</sup>, insulin pump therapy<sup>106</sup>, and more recently the advent of CGM<sup>107</sup>. While hypoglycemia continues to be the most important barrier to tight glycemic control, the increased use of insulin pumps or non-peaking basal insulin have decreased this risk<sup>108</sup> and consistent use of CGM technology has the potential for further reductions in hypoglycemic events<sup>96</sup>.

Furthermore, there are data to suggest that care for T1D has improved as evidenced by reduced rates of microvascular disease in the past decades<sup>109–111</sup>, whereas data on CVD suggest that substantially less progress has been made in reduction of macrovascular disease rates<sup>111–113</sup>. That said, the DCCT/EDIC study has shown that intensive glycemic control over a mean of 6.5 years reduced CVD complications by 57% after a mean of 17 years of follow-up<sup>100</sup>. To address the increased morbidity and mortality due to CVD in T1D, guidelines have been published<sup>84,114–118</sup> that address CVD risk factors in youth with T1D. All of these guidelines emphasize the importance of improved glycemic control to optimize cardiovascular health in youth with T1D, a topic we have reviewed recently with respect to dyslipidemia<sup>119</sup>.

In addition to glycemic control, hypertension and dyslipidemia are also important vascular disease risk factors with extensive data to support their role as targets to improve cardiovascular health in people with T1D<sup>120</sup>. Despite abundant data on the importance of control of blood pressure and dyslipidemia, adequate control of these vascular disease risk factors is frequently not achieved<sup>121,122</sup>. There are fewer data addressing these issues in children and adolescents<sup>119</sup>. Therefore, despite extensive data that support aggressive treatment of vascular disease risk factors (glycemia, blood pressure, and cholesterol, among

others) in adults with T1D, the question arises as to how these data in adults apply to youth with T1D and furthermore how CVD risk factors should be treated in youth with T1D.

Unfortunately, while the clinical care and outcomes of T1D continues to improve, early mortality in T1D remains as do questions on how to prevent this<sup>113</sup>. For patients diagnosed with T1D at <18 years of age between 1965–1979 and followed through 1994 the standardized mortality ratio (SMR) in Japan (n=1,408) and Finland (n=5,126) were 12.9 and 3.7, respectively<sup>123</sup>. A Norwegian cohort of 1,906 T1D patients diagnosed at <15 years of age between 1973–1982 (46,147 person-years) reported an SMR for all cause mortality of 4.0 with an SMR of 20 for ischemic heart disease. Acute metabolic complications of T1D were the most common cause of death <30 years of age<sup>124</sup>. Similarly, data from the UK report a hazard ratio of 3.7 for annual mortality rates for people with T1D compared to non-diabetics (8.0 v. 2.4/100,000 person-years) with CVD as the predominant cause of death<sup>125</sup>. EURODIAB has reported an SMR of 2.0 in 12 European countries that followed 28,887 children with T1D (141 deaths during 219,061 person-years) with a range of SMR from 0–4.7 among the countries included in the study<sup>126</sup>. The complications of T1D (Melendez-Ramirez, Richards, and Cefalu) and hypoglycemia (Cefalu) are reviewed elsewhere in this edition.

## Conclusions

Data from large epidemiologic studies worldwide indicate that the incidence of T1D has been increasing by 2–5% worldwide and that the prevalence of T1D is approximately 1 in 300 in the US by 18 years of age. Research on risk factors for T1D is an active area of research to identify genetic and environmental triggers that could potentially 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 find a cure for T1D. Epidemiologic studies have an important on-going role to investigate the complex causes, clinical care, prevention, and cure of T1D.

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**Table 1**

The SEARCH for Diabetes In Youth Study: Prevalence (Index Year 2001) and Incidence Rates (Incident Years 2002–2005 combined) of Type 1 Diabetes among 5 Race-Ethnicity Groups by Age Category<sup>3,5</sup>

Race-Ethnicity		Age Category				
		0–4 years	5–9 years	10–14 years	15–19 years	
NHW	Prevalence per 1,000 (95% CI)	0.38 (0.33, 0.44)	1.63 (1.53, 1.75)	2.56 (2.43, 2.70)	3.22 (3.07, 3.38)	
	Incidence per 100,000 (95% CI)	19.4 (17.8, 21.1)	30.1 (28.1, 32.2)	32.9 (30.9, 35.0)	11.9 (10.8, 13.2)	
AA	Prevalence per 1,000 (95% CI)	0.22 (0.14, 0.34)	0.90 (0.72, 1.11)	1.79 (1.55, 2.08)	2.32 (2.02, 2.66)	
	Incidence per 100,000 (95% CI)	12.0 (9.6, 14.8)	19.3 (16.3, 22.9)	21.3 (18.3, 24.8)	9.5 (7.4, 12.0)	
Hispanic	Prevalence per 1,000 (95% CI)	0.17 (0.12, 0.25)	0.70 (0.59, 0.84)	1.47 (1.30, 1.67)	1.71 (1.51, 1.94)	
	Incidence per 100,000 (95% CI)	10.2 (8.3, 12.6)	18.2 (15.5, 21.3)	18.4 (15.6, 21.5)	8.7 (6.8, 11.1)	
API	Prevalence per 1,000 (95% CI)	0.18 (0.11, 0.30)	0.34 (0.23, 0.49)	0.62 (0.47, 0.81)	0.93 (0.74, 1.16)	
	Incidence per 100,000 (95% CI)	5.2 (3.3, 8.0)	7.6 (5.3, 10.9)	9.1 (6.6, 12.5)	5.7 (3.8, 8.6)	
Navajo	Prevalence per 1,000 (95% CI)	0	0.16 (0.06, 0.41)	0.15 (0.06, 0.38)	0.43 (0.23, 0.79)	
	Incidence per 100,000 (95% CI)	1.15 (0.20, 6.49)	3.28 (1.11, 9.64)	1.95 (0.53, 7.10)	4.03 (1.57, 10.37)	