Reduced Prevalence of Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Young Children Participating in Longitudinal Follow-Up

Helena Elding Larsson, MD, PHD[1]
Kendra Vehik, PHD[2]
Ronny Bell, PHD[3]
Dana Dabelea, MD, PHD[4]
Lawrence Dolan, MD[5]
Catherine Pihoker, MD[6]
Mikael Knip, MD, PHD[7,8,9]
Riitta Veijola, MD, PHD[10]
Bengt Lindblad, MD, PHD[11]
Ulf Samuelsson, MD, PHD[12]
Reinhard Holl, MD[13]
Michael J. Haller, MD[14]
on behalf of the TEDDY Study Group, SEARCH Study Group, Swediabkids Study Group, DPV Study Group, and Finnish Diabetes Registry Study Group*

OBJECTIVE—Young children have an unacceptably high prevalence of diabetic ketoacidosis (DKA) at the clinical diagnosis of type 1 diabetes. The aim of this study was to determine whether knowledge of genetic risk and close follow-up for development of islet autoantibodies through participation in The Environmental Determinants of Diabetes in the Young (TEDDY) study results in lower prevalence of DKA at diabetes onset in children aged <2 and <5 years compared with population-based incidence studies and registries.

RESEARCH DESIGN AND METHODS—Symptoms and laboratory data collected on TEDDY participants diagnosed with type 1 diabetes between 2004 and 2010 were compared with data collected during the similar periods from studies and registries in all TEDDY-participating countries (U.S., SEARCH for Diabetes in Youth Study; Sweden, Swediabkids; Finland, Finnish Pediatric Diabetes Register; and Germany, Diabetes Patienten Verlaufsdokumenation [DPV] Register).

RESULTS—A total of 40 children younger than age 2 years and 79 children younger than age 5 years were diagnosed with type 1 diabetes in TEDDY as of December 2010. In children <2 years of age at onset, DKA prevalence in TEDDY participants was significantly lower than in all comparative registries (German DPV Register, $P < 0.0001$; Swediabkids, $P = 0.02$; SEARCH, $P < 0.0001$; Finnish Register, $P < 0.0001$). The prevalence of DKA in TEDDY children diagnosed at <5 years of age (13.1%) was significantly lower compared with SEARCH (36.4%) ($P < 0.0001$) and the German DPV Register (32.2%) ($P < 0.0001$) but not compared with Swediabkids or the Finnish Register.

CONCLUSIONS—Participation in the TEDDY study is associated with reduced risk of DKA at diagnosis of type 1 diabetes in young children.

Diabetes Care 34:2347–2352, 2011

Recent epidemiological studies indicate that the incidence of type 1 diabetes is increasing worldwide, with the greatest increase in children aged <5 years (1). Perhaps most alarming is that the diagnosis of type 1 diabetes in children aged <5 years is frequently associated with concurrent diabetic ketoacidosis (DKA) (2–4). Depending on the specific population studied and the definition of DKA used, the reported prevalence of DKA in children under 5 years of age at diagnosis varies between 17.3 and 54.5% (3,5–9) (Table 1). When even younger subsets of newly diagnosed patients with type 1 diabetes were evaluated, DKA prevalence has been reported to be as high as 39.7% in children aged <3 years (2) and as high as 60% in children aged <2 years at diagnosis (3).

Prevention of DKA would eliminate the potential morbidity and mortality associated with cerebral edema at diagnosis and may provide considerable cost savings by reducing days of hospitalization and use of intensive care units. Previous studies of autoantibody-positive children have demonstrated fewer episodes of DKA, reduced morbidity, and improved clinical care in children diagnosed through prospective screening and follow-up (10,11). In addition, the diagnosis of children at an earlier stage of the disease (i.e., without metabolic decompensation associated with DKA) may afford children the preservation of

From the [1]Department of Pediatrics, Skåne University Hospital, Lund University, Malmö, Sweden; the [2]Pediatric Epidemiology Center, University of South Florida, Tampa, Florida; the [3]Department of Epidemiology, Wake Forrest University, Winston-Salem, North Carolina; the [4]Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado; the [5]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; the [6]Department of Pediatrics, University of Washington, Seattle, Washington; the [7]Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; the [8]Folkhälsan Research Center, Helsinki, Finland; the [9]Department of Pediatrics, Tampere University Hospital, Tampere, Finland; the [10]Department of Pediatrics, University of Oulu, Oulu, Finland; the [11]Department of Pediatrics, The Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden; the [12]Department of Health and Environment, Linköping University, Linköping, Sweden; the [13]Institute of Epidemiology, University of Ulm, Ulm, Germany; and the [14]Department of Pediatrics, University of Florida, Gainesville, Florida.
Corresponding author: Helena Elding Larsson, helena.larsson@med.lu.se.
Received 31 May 2011 and accepted 17 August 2011.
DOI: 10.2337/dc11-1026
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1026/-/DC1.
H.E.L. and M.J.H. contributed equally to this work.
*A complete list of the members of the TEDDY Study Group, SEARCH Study Group, Swediabkids Study Group, DPV Study Group, and Finnish Diabetes Registry Study Group can be found in the Supplementary Data online.

Table 1—*Literature review of DKA at diagnosis in children under age 5 years*

Study country (reference)	Definition of DKA	Time of diabetes onset	DKA frequency % (*n*)		
			<2 years of age	<3 years of age	<5 years of age
SEARCH, U.S. (7)	4	2002–2004	NA	NA	37.3 (458)
Austria (3)	1	1989–2008	60 (185)	NA	43.7 (775)
Germany (5)	3	1987–1997	NA	NA	36.0 (470)
Germany and Austria (8)	1	1995–2007	NA	NA	26.5 (NA)
Canada (2)	5	1994–2000	NA	39.7% (390)	NA
Finland (6)	2	1992–2001	44.7[1], 54.2[2] (48)	NA	23.7[1], 29.3[2] (137)
U.S. (9)	1	1995–1998	NA	NA	54.5 (44)

NA, data not available. DKA defined as follows: 1 = pH <7.3; 2 = pH <7.3 and/or bicarbonate <15 mmol/L; 3 = pH <7.3 or bicarbonate <15 mmol/L and ketonuria; 4 = arterial or capillary pH <7.3/venous pH <7.25 or ICD 9 code 250.1 at discharge or DKA diagnosis mentioned in the medical charts; 5 = ICD 9 codes 250.1/250.2/250.3 from medical charts. Superscript numbers refer to DKA frequency calculated by DKA definitions 1 and 2.

remaining β-cell function, the opportunity to participate in intervention trials, and the possibility of fewer long-term complications (12).

Several ongoing studies are following children at high genetic risk of type 1 diabetes from birth (13,14). Some of these studies provide risk information to subjects whereas some do not initially inform parents about their child's type 1 diabetes risk. Intensive follow-up of children with genetic risk of type 1 diabetes in prospective studies, which includes ongoing provision of updated risk information, may increase awareness of symptoms and enable early diagnosis of diabetes and prevention of DKA (10). Additionally, routine assessments of HbA_{1c}, fasting plasma glucose, and oral glucose tolerance tests (OGTTs) in children with confirmed autoantibodies may allow diagnosis of type 1 diabetes prior to recognition of symptoms.

As such, the specific aim of this study was to determine if participation in a longitudinal study of the natural history of type 1 diabetes, The Environmental Determinants of Diabetes in the Young (TEDDY), in which the parents of young children (aged <5 years) are aware of their child's increased risk for developing the disease, resulted in lower rates of DKA at diagnosis of type 1 diabetes compared with recent and ongoing population-based incidence registry studies conducted in countries also participating in TEDDY. Specifically, we hypothesized that DKA prevalence in young children participating in TEDDY (<2 years and <5 years of age at diagnosis) would be lower than the DKA rates of children participating in an observational study, SEARCH for Diabetes in Youth in the U.S. (7) and national registries, Swediabkids (Sweden) (15), the Finnish Pediatric Diabetes Register (16), and the German Diabetes Patienten Verlaufsdokumenation (DPV) Register (8).

RESEARCH DESIGN AND METHODS

Participants

We compared symptoms and laboratory results collected for children participating in the TEDDY study (17) diagnosed with type 1 diabetes between 1 January 2004 and 31 December 2010 with data from the population-based SEARCH study and population based registries (Swediabkids, Finnish Pediatric Diabetes Register, and German DPV Register) from all participating countries in TEDDY for the same incident years (when available). In the TEDDY study, children with genetic risk of type 1 diabetes are followed intensively from 3 months of age. TEDDY is a multicenter study, with sites in Sweden, Finland, Germany, and the U.S. (Colorado, Washington, and Florida/Georgia). All children are screened at birth for type 1 diabetes HLA risk genotypes, and children at risk are followed. The aim of TEDDY is to determine environmental factors associated with the development of islet autoantibodies and type 1 diabetes in children with increased genetic risk of the disease. Participating children are followed every third month from 3 months of age to measure height and weight, collect blood and stool samples, and obtain responses to a series of questionnaires. Blood samples at each visit are analyzed for autoantibodies against GAD, insulinoma associated protein 2, and insulin. In antibody-positive children, random plasma glucose and HbA_{1c} are measured at each visit. Additionally, autoantibody-positive children >3 years of age undergo OGTTs every 6 months. Parents are carefully informed about diabetes risk and provided with updated antibody results. Follow-up is intended to continue until subjects reach 15 years of age.

Collection of data at diagnosis of type 1 diabetes

At diagnosis of type 1 diabetes, data are collected from the treating physician using a standardized case report form requiring documentation that American Diabetes Association criteria for the diagnosis have been met (18). Data collection includes information on symptoms and parameters of metabolic decompensation, such as pH, urine ketones, blood ketones (betahydroxybutyrate), and electrolytes. Because routine care for children with type 1 diabetes varies considerably from site to site, the diagnosis form includes a free text area allowing study staff to extract information about the child's clinical status. This is critical for determining likely DKA status in children where no laboratory evaluation was performed. In some countries (i.e., Finland and Sweden), nearly all children diagnosed with type 1 diabetes have blood obtained for assessment of acid-base balance and are admitted to a hospital for inpatient care. In other countries, children without clinical signs of DKA and mild symptoms are preferentially treated as outpatients, and blood for evaluation of acid-base balance is only taken if the pediatrician suspects DKA or if the child is critically ill.

National registries for comparison

For comparative analyses of DKA at onset, we obtained data from national incidence studies being performed in the same countries as the TEDDY study (for the European registers during 2004–2009 and for the U.S. study during 2004–2005). Data were limited to children <5 years of age at diagnosis.

SEARCH for Diabetes in Youth (SEARCH). SEARCH is a U.S. multicenter study aimed at identifying prevalent and incident cases of diabetes among individuals <20 years of age at diagnosis. For these analyses, we included children diagnosed with type 1 diabetes in 2004 and 2005. DKA was defined in the SEARCH protocol using medical abstraction to identify bicarbonate <15 mmol/L or venous pH <7.25 (arterial/capillary pH <7.30), International Classification of Diseases, Ninth Revision, code 250.1, or physician's diagnosis of DKA. Our analysis included 275 SEARCH subjects diagnosed with type 1 diabetes when <5 years of age.

Swediabkids. Swediabkids is the Swedish pediatric national quality registry for type 1 diabetes, covering 100% of all children diagnosed in Sweden. The incidence register is part of this national online follow-up quality register for pediatric patients, where all pediatric diabetes clinic visits are recorded. In this report, we include data from 651 Swedish children diagnosed with type 1 diabetes between 2005 and 2009 and <5 years of age at diagnosis. Of those, 44 children were excluded from this analysis due to missing pH or bicarbonate values. DKA was defined as arterial pH <7.30 and severe if arterial pH was <7.10.

Finnish Diabetes Register. The Finnish Pediatric Diabetes Register was established in 2002 and collects data on all children in Finland diagnosed with type 1 diabetes. Diabetes was diagnosed according to World Health Organization criteria, and DKA was diagnosed as arterial pH <7.30 and considered severe if arterial pH was <7.10. In children without arterial pH or bicarbonate data, negative urine ketones, negative blood ketones, or lack of symptoms (polyuria, polydipsia, and polyphagia) were used to exclude DKA. Our analysis includes 737 children aged <5 years from the Finnish Diabetes Register diagnosed with type 1 diabetes from 2005 to 2009.

DPV. The German/Austrian diabetes documentation and quality management system (DPV) is a continuous diabetes data acquisition system providing data from 53,485 type 1 diabetes patients throughout Germany and Austria. DKA is defined in the DPV as arterial pH <7.30 and severe DKA as arterial pH <7.10. In patients without biochemical data, chart abstraction and physician attestation of the patient's condition at diagnosis is considered sufficient to rule out DKA. Our analysis includes 1,812 DPV children from the DPV diagnosed with diabetes from 2005 to 2009.

Definition of DKA

Because of differences in data collection and management of newly diagnosed patients within TEDDY, SEARCH, and the population-based registries, we used two definitions of DKA to ensure appropriate comparisons (Table 2). When comparing TEDDY data to the Swedish register, strict criteria for DKA were used and included arterial pH <7.30 (venous pH <7.25) or standardized bicarbonate <15 mmol/L. Severe DKA was defined as arterial pH <7.10 or standardized bicarbonate <5 mmol/L. For comparisons with SEARCH, German-DPV, and Finnish registers, broad criteria for DKA were used to include the strict criteria and, in cases where pH or bicarbonate values were missing, betahydroxybutyrate >3.0 mmol/L, urine ketones >40 mg/dL, or physician's diagnosis.

Statistical analysis

Data were analyzed using the Statistical Analysis System Software (Version 9.2; SAS Institute, Cary, NC). Prevalence estimates and 95% confidence intervals were calculated as the proportion presenting with DKA at the time of diagnosis by age-group (<2 and <5 years) based on appropriate definition (strict or broad). Rates were compared using χ^2 statistics or Fisher exact test (for small samples, less than or equal to five per cell) to assess overall differences in prevalence estimates by study.

RESULTS—TEDDY screened 424,788 children for type 1 diabetes HLA risk, identified 21,588 eligible subjects, and enrolled 8,677 children. As of 31 December 2010, 80 TEDDY subjects were diagnosed with type 1 diabetes (Supplementary Fig. 1). Of those, 40 children were <2 years of age and 79 were <5 years of age at diagnosis. The mean (range) HbA_{1c} (using National Glycohemoglobin Standardization Program standards) at diagnosis was 7.8% (5.0–13.3). Forty-three of the newly diagnosed children were males, and the median (range) age in months was 23.8 (8–55). Despite the relatively young age of the new onset cohort, 24 of 79 (30%) were asymptomatic at diagnosis. Of the asymptomatic children, 16 were from the general population (representing 29% of the newly diagnosed general population subjects) whereas 8 were from first degree–relative families (representing 33% of newly diagnosed first-degree relatives).

DKA in children <2 years of age

In children <2 years of age at diagnosis, 6 of 40 (15%) had DKA under the broad definition of DKA whereas 5 of 31 (16.1%) had DKA under the strict definition of DKA. TEDDY children diagnosed with type 1 diabetes before 2 years of age had lower rates of mild and total DKA when compared with population-based studies and registries (SEARCH, $P < 0.0001$; German DPV register, $P < 0.0001$;

Table 2—*Definitions of DKA*

Study/register	Definition of DKA
TEDDY	Strict definition: DKA, arterial pH <7.30 or bicarbonate <15 mmol/L; severe DKA, arterial pH <7.10 or bicarbonate <5 mmol/L. Broad definition: DKA, arterial pH <7.30 or bicarbonate <15 mmol/L. If pH and bicarbonate values missing, DKA was diagnosed if urine ketones >40 mg/dL, blood ketones >3.0 mmol/L, or by physician's diagnosis.
Swediabkids	DKA, arterial pH <7.30 (primary) or bicarbonate <15 (secondary); severe DKA, arterial pH <7.10 or bicarbonate <5 mmol/L.
SEARCH	DKA, bicarbonate <15 mmol/L, venous pH <7.25 or arterial pH <7.30 or International Classification of Diseases, Ninth Revision, code 250.1, or physician's diagnosis of DKA.
Finnish Pediatric Diabetes Registry	DKA, arterial pH <7.30; severe DKA, arterial pH <7.10. In children without pH or bicarbonate data, negative urine ketones, negative blood ketones, or lack of symptoms (polyuria, polydipsia, polyphagia) were used to exclude DKA.
German DPV Registry	DKA, arterial pH <7.30; severe DKA, arterial pH <7.10. In patients without biochemical data, chart abstraction and physician attestation of the patient's condition at diagnosis was used to exclude DKA.

Swediabkids, $P = 0.02$; Finnish register, $P = 0.0005$) (Table 3).

DKA in children <5 years of age

In children <5 years of age at diagnosis, 9 of 79 (11.3%) had DKA at diagnosis of diabetes under the broad definition of DKA. Using the strict definition of DKA and excluding those with insufficient data, 8 of 61 (13.1%) <5 years of age had DKA at diagnosis of diabetes.

Total DKA (mild and severe DKA) at diagnosis was significantly less common in TEDDY participants (11.3%) when compared with SEARCH (36.4%) ($P < 0.0001$) and German DPV (25.3%) ($P \leq 0.0001$) children, respectively, but were not statistically different from DKA at diagnosis for patients from the Swedish (16.9%) ($P = 0.45$) or Finnish (18.7%) ($P = 0.11$) registers.

Severe DKA

Although numbers were small, the rate of severe DKA (arterial pH <7.10) did not differ significantly between children diagnosed within the TEDDY study and those reported from national registries in any age-group. Notably, all three TEDDY children diagnosed with severe DKA were <2 years of age (8, 10, and 14 months, respectively) and had developed islet autoantibodies before clinical presentation of disease.

CONCLUSIONS—In this study we compared the prevalence of DKA in children participating in TEDDY and diagnosed with type 1 diabetes before the age of 5 years with national population-based registers. Our analyses demonstrate that TEDDY subjects diagnosed with type 1 diabetes before the age of 2 years experienced significantly less DKA at diagnosis (15%) when compared with new-onset patients reported in national diabetes registers from countries participating in TEDDY and the SEARCH study (35–50%). Similarly, TEDDY children diagnosed with type 1 diabetes before the age of 5 years experienced less DKA at onset when compared with children in the SEARCH study and the German DPV Registry, but not compared with children from the Finnish or Swedish registries. Although the relatively high proportion of TEDDY subjects who were first-degree relatives of type 1 diabetes patients may have confounded our analysis, DKA rates within the TEDDY cohort were similar among children recruited from the general population and those with a first-degree relative with type 1 diabetes, indicating that knowledge of diabetes risk and close longitudinal follow-up may be associated with reduced DKA risk regardless of family history.

Although our analysis is strengthened by the inclusion of data from a national incidence study and registries performed in each of the countries participating in TEDDY, we should note that children with incident diabetes from Colorado and Washington could have simultaneously been included in both the SEARCH and TEDDY databases, and the TEDDY participants in Sweden, Finland, and Germany could have been included in the national registries. While such an occurrence could have biased our data, the effect (given lower rates of DKA noted in TEDDY) would have been to mask the differences observed. As we were still able to document significant reductions in DKA when comparing TEDDY to SEARCH and the national registries, the effect of any potential bias was likely minimal. Unfortunately, we were unable to perform an analysis where participants in both TEDDY and a population-based study or registry were excluded.

Perhaps the most challenging issue related to inclusion of data from multiple national incidence registries was that of interpreting data with an appreciation of the different definitions of DKA used in each study (Table 2). The SEARCH study used a composite definition of DKA that includes standard cutoffs for pH and bicarbonate but also allows for nonbiochemical clinical documentation to account for DKA status. The Finnish and DPV registries used standard biochemical data, but excluded DKA in children with negative urine ketones, negative blood ketones, or lack of symptoms. Conversely, the Swedish registry relied entirely on biochemical data to document DKA status. For the purposes of this analysis, TEDDY defined DKA using both strict criteria (standard cutoffs for pH and bicarbonate) and broad criteria (allowing us to document DKA status on the basis of urine/blood ketones and clinician documentation).

When comparing overall DKA rates in TEDDY participants with children reported in the Swedish and Finnish registry, no significant differences were seen in children diagnosed before 5 years of age. However, rates of DKA in TEDDY participants aged <5 years were significantly lower when compared with children from the U.S. SEARCH study and the German registry. These observations are concordant with reports that countries with a high incidence of type 1 diabetes (Finland and Sweden) report reduced frequencies of DKA when compared with countries with lower incidence of type 1 diabetes. Decreased frequencies of DKA at onset of disease have been reported from Finland between 1982 and 2001, with a decrease from 22.4 to 15.2% in children 0–15 years of age and a decrease from 32.1 to 17.7% in children with onset before the age of 5 years (6). That said, the rate of DKA in children <2 years of age at onset remained unacceptably high (39.1%) (6). On the contrary, German data from the DPV register did not reveal reduced frequency of DKA in any age-group between 1995 and 2007 (8). In a Swedish study, the incidence of DKA at onset of type 1 diabetes in children diagnosed from 2000 to 2004 was 16%, with no difference reported between age-groups. However, children <2 years of age were not specifically analyzed (15).

The youngest children with new onset type 1 diabetes (<2 years of age) remain at high risk of DKA (Table 1) (6). More specifically, these young children are prone to severe DKA at onset. Of the children in TEDDY diagnosed with severe DKA (pH <7.10), all three were <2 years of age (8, 10, and 14 months, respectively). Although all three were antibody positive prior to diagnosis, we should note that because of the lag time from antibody testing to reporting of results, the parents of these children were likely not informed of the antibody status prior to the diagnosis. As such, rapid analysis and reporting of antibody status in high-risk children could further aid in reducing DKA rates.

Unfortunately, our analysis lacked the power to determine if participation in TEDDY reduced the risk of severe DKA in children <2 years of age. That said, the observation of reduction in overall DKA in the youngest patients with new-onset diabetes suggests that participation in a longitudinal natural history study with provision of updated autoantibody risk information, frequent follow-up, and scheduled laboratory evaluations (autoantibodies, HbA_{1c}, glucose, and OGTT) to diagnose asymptomatic cases is associated with reduced DKA risk. Although potentially cost prohibitive outside the constraints of a research protocol, combined approaches to educate communities on signs and symptoms of DKA (as in the Parma, Italy experiments) and to provide genetic or antibody screening to further identify high-risk subjects may eventually be required to achieve the goal of entirely preventing DKA in children.

Table 3—*DKA rates in children aged <5 years and <2 years at diagnosis*

	Total DKA				Mild DKA				Severe DKA			
Study	<2 years**	*P* value	<5 years**	*P* value	<2 years**	*P* value	<5 years**	*P* value	<2 years**	*P* value	<5 years**	*P* value
TEDDY (strict DKA definition)*	5/31 16.1% (6.1–34.5)	—	8/61 13.1% (6.2–24.8)	—	2/31 6.5% (1.1–22.8)	—	5/61 8.2% (3.1–18.8)	—	3/31 9.7% (2.5–26.9)	—	3/61 4.9% (1.3–14.6)	—
TEDDY (broad DKA definition)Ŧ	6/40 15% (6.3–30.5)	—	9/79 11.3% (5.7–21.0)	—	3/40 7.5% (2.0–21.5)	—	6/79 7.6% (3.1–16.4)	—	3/40 7.5% (2.0–21.5)	—	3/79 3.8% (0.9–11.5)	—
Sweden registry*	51/129 39.5% (31.2–48.6)	0.02	102/604 16.9% (14.0–20.2)	0.45	39/129 30.2% (22.6–39.0)	0.005	78/604 12.9% (10.4–15.9)	0.41	12/129 9.3% (5.1–16.0)	1	24/604 4.0% (2.6–5.9)	0.73
SEARCHŦ	29/58 50.0% (36.7–63.3)	<0.0001	100/275 36.4% (30.7–42.4)	<0.0001	NA	NA	NA	NA	NA	NA	NA	NA
Finland registryŦ	82/183 44.8% (37.5–52.3)	<0.0001	138/737 18.7% (16.0–21.8)	0.11	64/183 35.0% (28.1–42.4)	0.0005	114/737 15.5% (12.9–18.1)	0.06	18/183 9.8% (5.9–15.1)	0.77	24/737 3.3% (2.1–4.8)	0.74
German registryŦ	235/435 54% (49.2–58.8)	<0.0001	583/1,812 32.2% (30.0–34.4)	<0.0001	171/435 39.3% (34.7–44.1)	<0.0001	458/1,812 25.3% (23.3–27.4)	<0.0001	64/435 14.7% (11.6–18.5)	0.34	125/1,812 6.9% (5.8–8.2)	0.36

NA, data not available. ***N* cases/sample population denominator, prevalence (95% confidence intervals). *All comparisons made to TEDDY strict definition. ŦAll comparisons made to TEDDY broad definition.

DKA is a serious condition with high morbidity and risk of developing cerebral edema (for a review see Levin [19]). Children diagnosed with DKA are hospitalized and often treated in intensive care units. An early diagnosis of diabetes would therefore be directly beneficial to the child and indirectly beneficial to society through reduction of morbidity, mortality, and cost at onset of disease. Additionally, early diagnosis and aggressive management of diabetes may be beneficial in allowing for the presence of a larger functioning β-cell mass, easier metabolic control, and possible reductions in long-term complication risk (12,20). Children diagnosed in an early stage of disease may also be eligible to participate in intervention trials aimed at protecting remaining β-cell mass.

In conclusion, intensive longitudinal follow-up and continuous education regarding diabetes risk, as provided in diabetes prediction studies such as TEDDY, may yield direct benefit to young children diagnosed with type 1 diabetes through early diagnosis and reduction of DKA risk. Ongoing efforts to reduce and eliminate DKA at diagnosis in young children are urgently needed.

Acknowledgments—TEDDY is funded by DK-63829, -63861, -63821, -63865, -63863, -63836, and -63790 and Contract HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, Juvenile Diabetes Research Foundation, and Centers for Disease Control and Prevention. SEARCH for Diabetes in Youth is funded by the Centers for Disease Control and Prevention (PA numbers 00097, DP-05-069, and DP-10-001) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases. Funding for DPV initiative was provided by Bundesministerium fuer Bildung und Forschung Competence Net Diabetes (FKZ 01GI0859). The site contract numbers are as follows: Kaiser Permanente Southern California, U48/CCU919219, U01 DP000246, and U18DP002714; University of Colorado Denver, U48/CCU819241-3, U01 DP000247, and U18DP000247-06A1; Kuakini Medical Center, U58CCU919256 and U01 DP000245; Children's Hospital Medical Center (Cincinnati), U48/CCU519239, U01 DP000248, and 1U18DP002709; University of North Carolina at Chapel Hill, U48/CCU419249, U01 DP000254, and U18DP002708-01; University of Washington School of Medicine, U58/CCU019235-4, U01 DP000244, and U18DP002710-01; Wake Forest University School of Medicine, U48/CCU919219, U01 DP000250, and 200-2010-35171.

No potential conflicts of interest relevant to this article were reported.

H.E.L. wrote the manuscript. K.V. and R.B. researched data and reviewed and edited the manuscript. D.D. reviewed and edited the manuscript and contributed to discussion. L.D. and C.P. reviewed and edited the manuscript. M.K. researched data, reviewed and edited the manuscript, and contributed to discussion. R.V. reviewed and edited the manuscript. B.L. researched data and reviewed and edited the manuscript. U.S. reviewed and edited the manuscript. R.H. researched data and reviewed and edited the manuscript. M.J.H. wrote the manuscript.

References

1. Gale EA. The rise of childhood type 1 diabetes in the 20th century. Diabetes 2002;51:3353–3361
2. Bui H, To T, Stein R, Fung K, Daneman D. Is diabetic ketoacidosis at disease onset a result of missed diagnosis? J Pediatr 2010;156:472–477
3. Schober E, Rami B, Waldhoer T; Austrian Diabetes Incidence Study Group. Diabetic ketoacidosis at diagnosis in Austrian children in 1989-2008: a population-based analysis. Diabetologia 2010;53:1057–1061
4. Cody D. Infant and toddler diabetes. Arch Dis Child 2007;92:716–719
5. Neu A, Willasch A, Ehehalt S, Hub R, Ranke MB; DIARY Group Baden-Wuerttemberg. Ketoacidosis at onset of type 1 diabetes mellitus in children—frequency and clinical presentation. Pediatr Diabetes 2003;4:77–81
6. Hekkala A, Knip M, Veijola R. Ketoacidosis at diagnosis of type 1 diabetes in children in northern Finland: temporal changes over 20 years. Diabetes Care 2007;30:861–866
7. Rewers A, Klingensmith G, Davis C, et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008;121:e1258–e1266
8. Neu A, Hofer SE, Karges B, Oeverink R, Rosenbauer J, Holl RW; DPV Initiative and the German BMBF Competency Network for Diabetes Mellitus. Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicenter analysis of 14,664 patients from 106 institutions. Diabetes Care 2009;32:1647–1648
9. Mallare JT, Cordice CC, Ryan BA, Carey DE, Kreitzer PM, Frank GR. Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. Clin Pediatr (Phila) 2003;42:591–597
10. Barker JM, Goehrig SH, Barriga K, et al.; DAISY study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. Diabetes Care 2004;27:1399–1404
11. Triolo TM, Chase HP, Barker JM; DPT-1 Study Group. Diabetic subjects diagnosed through the Diabetes Prevention Trial-Type 1 (DPT-1) are often asymptomatic with normal A1C at diabetes onset. Diabetes Care 2009;32:769–773
12. Ludvigsson J. Immune intervention at diagnosis—should we treat children to preserve beta-cell function? Pediatr Diabetes 2007;8(Suppl. 6):34–39
13. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers associated with IDDM: diabetes autoimmunity study in the young (DAISY). Diabetologia 1996;39:807–812
14. Nejentsev S, Sjöroos M, Soukka T, et al. Population-based genetic screening for the estimation of type 1 diabetes mellitus risk in Finland: selective genotyping of markers in the HLA-DQB1, HLA-DQA1 and HLA-DRB1 loci. Diabet Med 1999;16:985–992
15. Hanas R, Lindgren F, Lindblad B. Diabetic ketoacidosis and cerebral oedema in Sweden—a 2-year paediatric population study. Diabet Med 2007;24:1080–1085
16. Hekkala A, Reunanen A, Koski M, Knip M, Veijola R; Finnish Pediatric Diabetes Register. Age-related differences in the frequency of ketoacidosis at diagnosis of type 1 diabetes in children and adolescents. Diabetes Care 2010;33:1500–1502
17. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) Study. Ann N Y Acad Sci 2008;1150:1–13
18. American Diabetes Association. Executive summary: standards of medical care in diabetes—2011. Diabetes Care 2011;34 (Suppl. 1):S4–S10
19. Levin DL. Cerebral edema in diabetic ketoacidosis. Pediatr Crit Care Med 2008;9:320–329
20. Bowden SA, Duck MM, Hoffman RP. Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. Pediatr Diabetes 2008;9:197–201