Diabetic Ketoacidosis at Diabetes Onset: Still an All Too Common Threat in Youth

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Objective To define the demographic and clinical characteristics of children at the onset of type 1 diabetes (T1D), with particular attention to the frequency of diabetic ketoacidosis (DKA).

Study design The Pediatric Diabetes Consortium enrolled children with new-onset T1D into a common database. For this report, eligible subjects were aged <19 years, had a pH or HCO_3 value recorded at diagnosis, and were positive for at least one diabetes-associated autoantibody. Of the 1054 children enrolled, 805 met the inclusion criteria. A pH of <7.3 and/or HCO_3 value of <15 mEq/L defined DKA. Data collected included height, weight, hemoglobin A1c, and demographic information (eg, race/ethnicity, health insurance status, parental education, family income).

Results The 805 children had a mean age of 9.2 years, 50% were female; 63% were non-Hispanic Caucasian. Overall, 34% of the children presented in DKA, half with moderate or severe DKA (pH <7.2). The risk for DKA was estimated as 54% in children aged <3 years and 33% in those aged ≥3 years ($P = .006$). In multivariate analysis, younger age ($P = .002$), lack of private health insurance ($P < .001$), African-American race ($P = .01$), and no family history of T1D ($P = .001$) were independently predictive of DKA. The mean initial hemoglobin A1c was higher in the children with DKA compared with those without DKA (12.5% ± 1.9% vs 11.1% ± 2.4%; $P < .001$).

Conclusion The incidence of DKA in children at the onset of T1D remains high, with approximately one-third presenting with DKA and one-sixth with moderate or severe DKA. Increased awareness of T1D in the medical and lay communities is needed to decrease the incidence of this life-threatening complication. *(J Pediatr 2013;162:330-4)*.

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication of type 1 diabetes (T1D) that represents the major diabetes-related morbidity and mortality in youth with T1D.[1,2] Before a diagnosis of T1D, family members may be unaware of the symptoms of hyperglycemia, and medical care providers may assign more benign diagnoses to these symptoms, further delaying treatment. When the diagnosis of T1D is not made on the initial visit to a medical care provider, the risk of the child developing DKA at onset increases significantly.[3,4] Physicians' increased awareness and understanding of the risk of DKA in children and adolescents with new-onset T1D, especially young children, may ultimately lead to a decrease in DKA at diagnosis.

The Pediatric Diabetes Consortium (PDC), comprising 7 pediatric diabetes centers, was established to improve the care of children and adolescents by sharing best current practices through the prospective collection of common outcome data using standardized case report forms. The first project undertaken by the PDC was to accumulate a cohort of children and adolescents with T1D that would be followed prospectively from the time of diagnosis at all participating centers. A major impetus for this study was the lack of recent data on presenting clinical features and outcomes of treatment during the first 12-24 months of therapy of US youth with T1D.[5] In the present study, we examined the incidence of DKA in our cohort at the time of diagnosis, the clinical characteristics associated with DKA, and the demographic and socioeconomic factors associated with presenting with DKA at onset of T1D.

BMI	Body mass index
DAA	Diabetes-associated autoantibody
DKA	Diabetic ketoacidosis
HbA1c	Hemoglobin A1c
PDC	Pediatric Diabetes Consortium
SES	Socioeconomic status
T1D	Type 1 diabetes

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Methods

The PDC cohort was enrolled at 7 US pediatric diabetes centers between July 2009 and April 2011. The protocol was approved by the Institutional Review Board of each participating center. Written informed consent was obtained from participants aged ≥18 years and from parents of children aged <18 years. Written assent also was obtained from younger youth in accordance with local Human Subjects Investigational Review Board guidelines. Inclusion criteria for this analysis required age <19 years at diagnosis of T1D, presence of at least one positive diabetes-associated autoantibody (DAA), receipt of care at a PDC center within 90 days of diagnosis, and information available to determine whether DKA was present at the time of diagnosis. Of the 1054 enrolled subjects, 828 were positive for at least one positive DAA, and 805 also had sufficient clinical and laboratory data available to determine DKA status at diagnosis. Information with respect to participant demographics, socioeconomic status (SES), and clinical characteristics, including diagnosis of T1D, were retrieved from medical records and from participant and/or parent interviews.

The criteria for diagnosis of DKA included venous pH <7.3 or HCO_3 <15 mEq/l. This relatively broad definition of DKA was used by the Diabetes Control and Complications Trial and later agreed upon by the American Diabetes Association, the Pediatric Endocrine Society, and the European Endocrine Society, although these societies have adopted definitions with slight differences in venous pH cutoff, <7.25 or <7.3.[6-8] A recent comparison of pH and serum HCO_3 levels in 300 children with diagnosed DKA confirmed that a serum HCO_3 ≤18.5 predicts a pH <7.3; thus, a serum HCO_3 level of <15 mg/dL is a conservative criterion for acidosis.[9] Data collection for the present study included both pH and HCO_3 in most cases, but in some cases we were unable to confirm that the samples were collected concurrently. Thus, we included in our DKA cohort all individuals with either a diagnostic pH or a diagnostic HCO_3 level. The 277 study subjects who met one or both of the foregoing clinical criteria for DKA. The hemoglobin A1c (HbA1c) measurement obtained closest to the date of diagnosis (within ±14 days) was used in this analysis.

Body mass index (BMI) was computed from the height and weight measurements obtained closest to the date of diagnosis (within ±60 days). BMI percentile adjusted for age and sex was calculated for each subject using Centers for Disease Control and Prevention data for the general population.[10] DAA testing performed any time before diagnosis or within 91 days after diagnosis for insulinoma-associated autoantibody or glutamic acid decarboxylase autoantibody and within 14 days after diagnosis for insulin autoantibody were included.

Logistic regression analysis was used to evaluate the following risk factors for DKA at the time of diagnosis: age, sex, race/ethnicity, health insurance, family income, parental education, family structure, familial diabetes, BMI, HbA1c, and PDC center. A multivariate model was constructed using stepwise selection. Covariates with $P < .10$ were retained in the model, but only factors with $P < .01$ were considered statistically significant owing to multiple comparisons. Continuous variables (age and HbA1c) were tested for linearity by adding a quadratic term to the model. If significant nonlinearity was detected, then the variable was divided into categories and analyzed as discrete. Interaction terms were tested for all variables included in the final multivariate model, with $P < .01$ required for consideration for inclusion.

Because the SES factors (ie, health insurance, family income, caregiver education, and family structure) were highly correlated, it was not possible to distinguish all of their associations with DKA in multivariate analysis. Sensitivity analyses were performed with additional multivariate models including various subsets of the SES factors (even when $P > .10$), to assess their impact on the results.

Covariates with missing values were excluded from univariate analysis. For multivariate analysis, missing covariates were treated as a separate category for discrete variables, and a missing value indicator was added to the model for continuous variables. All of the reported P values are 2-sided. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

The 805 children included in our analysis ranged in age at the time of diagnosis from 7.9 months to 18.1 years and had a mean age of 9.2 years. The study cohort was 50% female, 63% non-Hispanic Caucasian, 22% Hispanic, and 8% non-Hispanic black, and 7% had a parent or sibling with T1D. Family income and parental education were relatively high in the participants who provided this information, and the majority had some form of health insurance.

Overall, 34% of participants presented in DKA (n = 277), ranging from 28% to 40% across the 7 centers ($P = .19$). pH data were available for 251 of these 277 participants, showing that 51% were in moderate or severe DKA, 22% with a pH <7.1 and 29% with a pH of 7.1 to <7.2 (**Table I**). Serum HCO_3, available in 263 participants, ranged from 2 to 26 mEq/L, with 8% at <5 mEq/L and 40% at 5 to <10 mEq/L. Of the 237 participants with both pH and serum HCO_3 data available, 8% had compensated acidosis (HCO_3 <15 and pH ≥7.3) and 13% had an initial HCO_3 ≥15 and initial pH <7.3, perhaps related to the differing times of serum sample collection (**Figure 1**; available at www.jpeds.com). Reported glucose levels for the participants presenting with DKA (n = 263) ranged from 191 to 1500 mg/dL, with 10% at <300 mg/dL, 38% at 300 to <500 mg/dL, 32% at 500 to <700 mg/dL, and 20% at ≥700 mg/dL (**Figures 2** and **3**; available at www.jpeds.com).

The children presenting with DKA were younger than those without DKA (mean age, 8.8 years vs 9.4 years), reflecting the greatly increased risk for DKA in the youngest