Predictors of Acute Complications in Children With Type 1 Diabetes

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Diabetic ketoacidosis (DKA) and severe hypoglycemia are acute complications of type 1 diabetes in children. Both are theoretically preventable. The incidence of DKA and severe hypoglycemia have been reported largely by studies completed before 1993. However, less is known about the incidence and predictors for DKA and severe hypoglycemia in the US population in the era after the Diabetes Control and Complications Trial (DCCT). Few of the previous studies examined predictors for DKA and severe hypoglycemia in children and even fewer used a prospective design.

Diabetic ketoacidosis often leads to an emergency department (ED) visit and hospital admission and contributes to the high costs of care for children with type 1 diabetes. Cerebral edema, a devastating complication of DKA, is one of the leading causes of mortality among children with type 1 diabetes. The prevalence of DKA has been estimated to be up to 30% among the patients newly diagnosed with diabetes, but the incidence of DKA later in the clinical course of the disease is less documented. The incidence of DKA in adolescent patients enrolled in the DCCT was 2.8 per 100 patient-years in the intensive treatment group (n = 92) vs 4.7 per 100 patient-years in the conventional therapy group (n = 103).

The true incidence of severe hypoglycemia is also unknown. Previous studies, based on different definitions of severe hypoglycemia, provided rates.

Context: Diabetic ketoacidosis and severe hypoglycemia are acute complications of type 1 diabetes that are related, respectively, to insufficient or excessive insulin treatment. However, little is known about additional modifiable risk factors.

Objective: To examine the incidence of ketoacidosis and severe hypoglycemia in children with diabetes and to determine the factors that predict these complications.

Design, Setting, and Participants: A cohort of 1243 children from infancy to age 19 years with type 1 diabetes who resided in the Denver, Colo, metropolitan area were followed up prospectively for 3994 person-years from January 1, 1996, through December 31, 2000.

Main Outcome Measures: Incidence of ketoacidosis leading to hospital admission or emergency department visit and severe hypoglycemia (loss of consciousness, seizure, or hospital admission or emergency department visit).

Results: The incidence of ketoacidosis was 8 per 100 person-years and increased with age in girls (4 per 100 person-years in <7; 8 in 7-12; and 12 in ≥13 years; P < .001 for trend). In multivariate analyses, sex-adjusted and stratified by age (<13 vs ≥13 years), the risk of ketoacidosis in younger children increased with higher hemoglobin A1c (HbA1c) (relative risk [RR], 1.68 per 1% increase; 95% confidence interval [CI], 1.45-1.94) and higher reported insulin dose (RR, 1.40 per 0.2 U/kg per day; 95% CI, 1.20-1.64). In older children, the risk of ketoacidosis increased with higher HbA1c (RR, 1.43; 95% CI, 1.30-1.58), higher reported insulin dose (RR, 1.13; 95% CI, 1.02-1.25), underinsurance (RR, 2.18; 95% CI, 1.65-2.95), and presence of psychiatric disorders (for boys, RR, 1.59; 95% CI, 0.96-2.65; for girls, RR, 3.22; 95% CI, 2.25-4.61). The incidence of severe hypoglycemia was 19 per 100 person-years (<.001 for trend) and decreased with age in girls (24 per 100 patient-years in <7, 19 in 7-12, and 14 in ≥13 years). In younger children, the risk of severe hypoglycemia increased with diabetes duration (RR, 1.39 per 5 years; 95% CI, 1.16-1.69) and underinsurance (RR, 1.33; 95% CI, 1.08-1.65). In older children, the risk of severe hypoglycemia increased with duration (RR, 1.34; 95% CI, 1.25-1.51), underinsurance (RR, 1.42; 95% CI, 1.11-1.81), lower HbA1c (RR, 1.22; 95% CI, 1.12-1.32), and presence of psychiatric disorders (RR, 1.56; 95% CI, 1.23-1.98). Eighty percent of episodes occurred among the 20% of children who had recurrent events.

Conclusions: Some children with diabetes remain at high risk for ketoacidosis and severe hypoglycemia. Age- and sex-specific incidence patterns suggest that ketoacidosis is a challenge in adolescent girls while severe hypoglycemia continues to affect disproportionately the youngest patients and boys of all ages. The pattern of modifiable risk factors indicates that underinsured children and those with psychiatric disorders or at the extremes of the HbA1c distribution should be targeted for specific interventions.
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ranging from 3.1 to 85.7 episodes per 100 patients per year.²⁵ The DCCT found that intensive insulin treatment in adolescent patients increased the frequency of severe hypoglycemia (26.7 per 100 patient-years) almost 3 times more than that observed in those receiving conventional therapy (9.7 per 100 patient-years).²¹,²² The incidence of hypoglycemia continues to be high even in those with poor glycemic control and hemoglobin A₁c (HbA₁c) levels higher than 9%.⁹

Poor glycemic control, family and school problems, low socioeconomic status, ethnicity, sex, and lack of adequate health insurance have been reported to increase risk of acute complications in children with type 1 diabetes.⁹,¹⁰,²⁴ However, these predictors have not been sufficiently characterized to allow for effective preventive programs.²⁵

The purpose of this study was to determine the incidence and the predictors of DKA and severe hypoglycemia in a large cohort of children with type 1 diabetes. We hypothesized that the incidence of DKA and severe hypoglycemia in children with type 1 diabetes remains high, despite improvements in diabetes care. In addition, we hypothesized that underinsurance (a surrogate for low socioeconomic status) and the presence of psychiatric disorders predict DKA and severe hypoglycemia, independently of demographic factors, duration of diabetes, and the level of glycemic control. If confirmed, these modifiable risk factors could be targeted in intervention programs aimed at preventing acute diabetic complications.

METHODS
Study Design
In 1993, a comprehensive computerized patient record system was established at the Barbara Davis Center for Childhood Diabetes, Denver, Colo, to evaluate prospectively selected diabetes-related outcomes in relation to risk factors, treatment patterns, and comorbidity. This system was expanded in 1995. For this study, we selected a cohort of 1243 children (583 girls, 660 boys) who met the following inclusion criteria: (1) diagnosis of diabetes (not secondary to other conditions) and continuous insulin treatment, (2) in infancy to age 19 years at the last visit, (3) residence in the 6-county Denver metropolitan area, and (4) at least 1 outpatient visit at the Barbara Davis Center during the study period January 1, 1996, through December 31, 2000. This study was approved by the Colorado multiple institutional review board.

The median age of participants was 13.0 years (interquartile range [IQR], 9.0-16.0 years). The median age at diagnosis was 7.0 years (IQR=4.0-11.0 years) and the median duration of diabetes at the half point of the follow-up period was 3.3 years (IQR, 1.2-7.0 years). An average patient had 12 diabetes clinic visits and a median follow-up period of 3.5 years (IQR, 1.7-4.9 years). The information regarding acute events, HbA₁c levels, insulin dose, insurance status, body mass index (BMI), and comorbidities was collected at each visit. Prior to study completion, 13.8% of the participants were lost to follow-up (1.3% in 1996, 1.5% in 1997, 1.9% in 1998, 5.1% in 1999, and 4.0% in 2000), mostly because their families had moved out of state.

Outcome Measures
Acute events were identified by interview at the time of each visit and recorded in a computerized record system.

Diabetic ketoacidosis was defined as an episode of hyperglycemia and ketoadidosis leading to an ED visit and/or hospital admission. The episodes of DKA at the onset of diabetes were excluded. Computerized patient record data were verified retrospectively by reviewing medical records at The Children’s Hospital in Denver, where most of the admissions occurred. We reviewed charts of 100 children, randomly chosen from among 274 children hospitalized at the children’s hospital with an International Classification of Diseases, Ninth Revision, code 250.1 hospital admission between 1996 and 2000. Detailed review of these charts identified 148 potential DKA episodes. Of the 42 episodes at diabetes onset, 12 who lived outside the study area and 17 who were not Barbara Davis Center patients were excluded. The remaining 77 admissions were matched with the patient clinic records. The study-patient records were found to be 92% (71/77) complete in recording a possible DKA episode. Next, we applied the DCCT definition of DKA to the 77 patients admitted to the children’s hospital, including (1) blood glucose level higher than 250 mg/dL (>13 mmol/L); (2) presence of large or moderate ketone level in urine or serum; and (3) arterial blood pH level lower than 7.30, venous blood pH level lower than 7.25, or serum bicarbonate lower than 15 mEq/L. Of the 71 episodes found in records at both institutions, 67 (94%) met the definition. Of the 6 records found only in the children’s hospital, 5 met the definition. In summary, we found documentation of DKA in the electronic patient records to be 92% complete and 94% accurate.

Severe hypoglycemia was defined as a hypoglycemic episode leading to loss of consciousness or seizure or resulting in an ED visit or hospital admission. A validation study of the completeness of hypoglycemic events documentation in the patient record has been previously published.²⁷

Briefly, families of 884 patients treated at the Barbara Davis Center completed a questionnaire designed to ascertain all episodes of hypoglycemia that occurred during the years 1993 through 1998. The DCCT definition of severe and milder episodes of hypoglycemia were used to develop the questionnaire. After reviewing records from 1993 through 1998, we found that the 11,221 computerized clinical records of the 884 patients were 98% complete for severe and 62% complete for milder hypoglycemic events. Because the DCCT definition of milder episodes includes “episodes requiring assistance” are difficult to standardize in young children, we included only severe hypoglycemic events in our study.
Definitions of Selected Predictors

Underinsurance was defined as a lack of insurance, receiving Medicaid, participating in the Colorado Resident Discount Program, or having Child Health Plan Plus insurance. We used underinsurance as a main indicator of low socioeconomic status because it is easier to ascertain and standardize insurance coverage over time than it is to determine a family’s income or educational level, level of dysfunction, or other resources.

Psychiatric disorder was defined as having 1 or more of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I and Axis II diagnoses, including major depression, bipolar, anxiety, or panic disorder and/or use of psychotropic medication at any time during the study period. Attention deficit hyperactivity disorder and eating disorders were not included in this definition. Major psychiatric disorders were selected because of previous clinical observations that they may reflect systematically missed insulin injections, missed meals, infrequent blood glucose testing, suicidal attempts, chaotic lifestyle, and lack of compliance.4

The mean insulin dose (per kilogram of body weight) and the mean HbA1c level (measured in percentage) during the study period were calculated for each patient after excluding data from the initial year after diagnosis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis

Statistical analyses of the data were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC). Incidence rates of DKA and severe hypoglycemia were calculated by summing the number of events that occurred during the follow-up and dividing by total person-years of follow-up and presented per 100 person-years. Medians and IQRs were calculated for the demographic and laboratory patient characteristics and are reported in Table 1 and Table 2.

We identified predictors of severe hypoglycemia, using univariate and multivariate Poisson regression of the counts of severe hypoglycemia. This was done using PROC GENMOD function in the SAS software program. In these Poisson regressions, variable follow-up times were accounted for by using offset equal to the logarithm of the follow-up times. The same methods were carried out to determine predictors of DKA. Regression models were sex adjusted and stratified by age (<13 vs ≥13 years) because of significant interactions between

Table 1. Characteristics of Patients With Diabetic Ketoacidosis*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Diabetic Ketoacidosis Episodes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1048</td>
<td>134</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>13.0 (9.0-16.0)</td>
<td>13.0 (11.0-16.0)</td>
</tr>
<tr>
<td>Girls, %</td>
<td>45.5</td>
<td>53.7</td>
</tr>
<tr>
<td>Non-Hispanic white, %</td>
<td>78.9</td>
<td>77.6</td>
</tr>
<tr>
<td>Duration of diabetes, median (IQR), y</td>
<td>3.0 (0.7-7.0)</td>
<td>3.9 (2.3-7.5)</td>
</tr>
<tr>
<td>Hemoglobin A1c, median (IQR), %</td>
<td>8.8 (8.2-9.6)</td>
<td>9.5 (8.7-10.5)</td>
</tr>
<tr>
<td>Insulin dose, median (IQR), U/kg per day</td>
<td>0.85 (0.67-1.03)</td>
<td>0.89 (0.74-1.11)</td>
</tr>
<tr>
<td>Body mass index, median (IQR), kg/m²</td>
<td>20.5 (17.6-23.3)</td>
<td>20.0 (18.2-22.9)</td>
</tr>
<tr>
<td>Psychiatric disorders, %</td>
<td>9.6</td>
<td>18.7</td>
</tr>
<tr>
<td>Underinsurance, %</td>
<td>19.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Comprehensive diabetes education at diagnosis, %</td>
<td>60.9</td>
<td>56.0</td>
</tr>
<tr>
<td>Clinical visits per year, %†</td>
<td>16.2</td>
<td>15.0</td>
</tr>
<tr>
<td>&lt;2</td>
<td>54.5</td>
<td>52.6</td>
</tr>
<tr>
<td>2-5</td>
<td>29.3</td>
<td>32.3</td>
</tr>
</tbody>
</table>

*Continuous variables are presented as median (interquartile range [IQR]) and are compared using the Kruskal-Wallis test. Categorical variables are compared using the χ² test. †Percentages may not sum to 100 due to rounding.

Table 2. Characteristics of Patients With Severe Hypoglycemia*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Severe Hypoglycemic Episodes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>908</td>
<td>160</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>13.0 (9.0-16.0)</td>
<td>12.5 (8.0-15.0)</td>
</tr>
<tr>
<td>Girls, %</td>
<td>47.4</td>
<td>46.9</td>
</tr>
<tr>
<td>Non-Hispanic white, %</td>
<td>76.4</td>
<td>81.9</td>
</tr>
<tr>
<td>Duration of diabetes, median (IQR), y</td>
<td>2.6 (0.5-9.5)</td>
<td>4.6 (2.7-7.8)</td>
</tr>
<tr>
<td>Hemoglobin A1c, median (IQR), %</td>
<td>8.0 (8.2-9.9)</td>
<td>8.2 (8.3-9.7)</td>
</tr>
<tr>
<td>Insulin dose, median (IQR), U/kg per day</td>
<td>0.9 (0.68-1.05)</td>
<td>0.8 (0.68-1.05)</td>
</tr>
<tr>
<td>Body mass index, median (IQR), kg/m²</td>
<td>20.7 (17.9-23.7)</td>
<td>20.1 (17.6-22.4)</td>
</tr>
<tr>
<td>Psychiatric disorders, %</td>
<td>10.4</td>
<td>15.0</td>
</tr>
<tr>
<td>Underinsurance, %</td>
<td>19.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Comprehensive diabetes education at diagnosis, %</td>
<td>61.7</td>
<td>55.0</td>
</tr>
<tr>
<td>Clinical visits per year, %†</td>
<td>17.5</td>
<td>15.1</td>
</tr>
<tr>
<td>&lt;2</td>
<td>49.6</td>
<td>62.3</td>
</tr>
<tr>
<td>2-5</td>
<td>32.9</td>
<td>22.6</td>
</tr>
</tbody>
</table>

*Continuous variables are presented as median (interquartile range [IQR]) and are compared using Kruskal-Wallis tests; categorical variables are compared using the χ² test.
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age and HbA1c level, mean insulin dose per kilogram, and diabetes duration.

Backwards stepwise logistic regression analysis was used to identify predictors of the recurrence of DKA or severe hypoglycemia after adjusting for the length of the follow-up. The Hosmer-Lemeshow goodness-of-fit test indicated very good fit for the models reported. There was little evidence of collinearity in inspection of tolerance warnings, SEs, and correlation matrix. Regression models were stratified by age (<13 vs ≥13 years) because of significant interactions of some independent variables with age. Generally, interaction terms were considered significant at P<.01. For DKA significant interactions between age and HbA1c was P=.06; psychiatric disorders, P=.01; insulin dose, P=.009; and race, P=.03. For severe hypoglycemia significant interactions between age and sex were P=.08; HbA1c, P<.001; and psychiatric disorders, P=.009.

RESULTS
Diabetic Ketoacidosis
There were 320 hospital admissions and/or ED visits due to DKA in the study cohort during 3994 person-years of follow-up. The overall incidence of DKA was 8 per 100 patient-years and increased significantly (P<.001 for trend) with age in girls (4 per 100 person-years in those aged <7, 8 in those 7-12, and 12 in those ≥13 years; P<.001 for trend), but not in boys (7 per 100 person-years in those aged <7, 5 in those 7-12, and 8 in those ≥13 years; Figure 1). Demographic and laboratory characteristics of patients with and without DKA are compared in Table 1. Using univariate analysis, female sex, longer duration of diabetes, higher mean HbA1c level, higher reported insulin dose, the presence of psychiatric disorders, and underinsurance predicted DKA.

The Poisson multivariate regression analysis to identify potentially modifiable predictors of DKA was age stratified and sex adjusted. Figure 2 summarizes factors found to be significantly and independently predictive of DKA. In younger children, the relative risk of DKA increased with higher HbA1c level (relative risk [RR], 1.68 per 1% increase; 95% confidence interval [CI], 1.45-1.94; P<.001) and with higher reported insulin dose (RR, 1.40 per 0.2 U/kg per day; 95% CI, 1.20-1.64; P<.001). In older children, the RR increased with higher HbA1c level (RR, 1.43 per 1% increase; 95% CI, 1.30-1.58; P<.001), higher reported insulin dose (RR, 1.13 per 0.2 U/kg per day; 95% CI, 1.02-1.25; P<.02), underinsurance (RR, 2.18; 95% CI, 1.65-2.95; P<.001), and the presence of psychiatric disorders in boys (RR, 1.59; 95% CI, 0.96-2.65) and especially in girls (RR, 3.22; 95% CI, 2.25-4.61; P<.01 for interaction).

Severe Hypoglycemia
There were 768 severe hypoglycemia events in the study cohort during 3994 person-years. The overall incidence of severe hypoglycemia was 19 per 100 patient-years and decreased significantly with age in girls (24 per 100 patient-years in those aged <7, 19 in those 7-12, and 14 in those ≥13 years; P<.001 for trend) but not in boys (23 per 100 patient-years in those aged <7, 22 in those 7-12, and 20 in those ≥13 years) (Figure 3). Demographic and laboratory characteristics of patients with and without severe hypoglycemia are compared in Table 2. Using univariate analysis, non-Hispanic white ethnicity, longer duration of diabetes, the presence of psychiatric disorders, and underinsurance predicted severe hypoglycemia.
The Poisson multivariate regression analysis to identify potentially modifiable predictors of severe hypoglycemia was age-stratified (<13 vs ≥13 and sex adjusted). Figure 4 summarizes factors found to be significantly and independently predictive of severe hypoglycemia risk, which for younger children increased with diabetes duration (RR, 1.39 per 5-year increment; 95% CI, 1.16-1.69; P = .001) and underinsurance (RR, 1.33; 95% CI, 1.08-1.65; P < .008). In older children, the risk increased with lower HbA1c level (RR, 1.22 per 1% decrease; 95% CI, 1.12-1.32; P < .001), duration (RR, 1.34 per 5-year increment; 95% CI, 1.25-1.51; P < .001), underinsurance (RR, 1.42; 95% CI, 1.11-1.81; P < .005), and the presence of psychiatric disorders (RR, 1.56; 95% CI, 1.23-1.98).

Reurrence of the Acute Events

Nearly 60% of DKA episodes occurred in 5% of children with recurrent events (≥2 episodes) while 79% of severe hypoglycemia episodes occurred among 14% of children who had recurrent events. A detailed characterization of these patients is presented in Table 1 and Table 2. Eighty percent of episodes of either event occurred among just 20% of children in the cohort. Factors predictive of recurrent DKA and severe hypoglycemia were evaluated in age-stratified multiple-logistic regression models, adjusted for sex and length of the follow-up.

In younger children, the recurrence of DKA was associated with higher levels of HbA1c (OR, 1.81 per 1% increase; 95% CI, 1.26-2.60; P < .001) and with higher reported insulin dose (OR, 1.62 per 0.2 U/kg per day; 95% CI, 1.10-2.38; P < .02). In older children, recurrence of DKA was associated with higher HbA1c (OR, 1.64 per 1% increase; 95% CI, 1.26-2.14; P < .001), higher reported insulin dose (OR, 1.63 per 0.2 U/kg per day; 95%, 1.18-2.24; P < .003), underinsurance (OR, 3.39; 95% CI, 1.57-7.34; P < .002), and the presence of psychiatric disorders (OR, 4.39; 95% CI, 2.05-9.40; P < .001).

Reurrence of severe hypoglycemia in younger children was not associated with any specific predictors. In older children, the recurrence of severe hypoglycemia was associated with diabetes duration (RR, 1.54 per 5-year increments; 95% CI, 1.13-2.10; P < .006), and underinsurance (RR, 1.93; 95% CI, 1.10-3.38; P < .03).

COMMENT

The advantages of our study include prospective design, large sample size (2-4 times larger than that of any previous prospective studies), and broad representation of patients of different age, ethnicity, socioeconomic status, and diabetes duration. However, the study is not strictly population-based, representing an estimated 80% of all children with type 1 diabetes living in the Denver metropolitan area. Future studies will have to address potential urban and rural differences in the risk for acute diabetic complications related to distance from tertiary pediatric diabetes centers. Although the design of our study minimized underreporting or misclassification of events, it has not eliminated these limitations completely due to multiple providers involved in data collection.

Few previous studies have validated completeness of event ascertainment using independent sources of information. In our study, the electronic patient record proved to be a complete and accurate source. On the other
hand, our data collection system, designed to capture in real time only major diabetes care outcomes, lacks detail concerning severity of acute events, related complications, and costs of care.

Accrual into the study continued throughout the observation period, and there has been a 14% loss to follow up. However, these factors were accounted for at the level of analyses by calculation of exact person-year denominators for participants affected by left or right censoring.

This is one of few studies to evaluate systematically potential predictors for DKA and severe hypoglycemia in children. In this study, children with type 1 diabetes, while managed by a state-of-the-art multidisciplinary team, still experienced significant numbers of severe, potentially preventable complications. The overall incidence of DKA, 8 per 100 patient-years, in this study population was higher than that reported in the highly selective DCCT population, but comparable observational studies before and after DCCT are summarized in Table 3.

Adolescent girls were at the highest risk for DKA, with the incidence rate of 12 per 100 patient-years consistent with previous reports. This could be related to issues of body image because adolescent girls with diabetes often omit insulin injections to lose weight. Girls with recurrent ketoacidosis have also been shown to exhibit more behavioral problems, lower social competence, and higher levels of family conflict. We found somewhat different predictors for DKA in prepubertal vs older children: poor glycemic control reflected by higher HbA1c and reported higher insulin dose predicted DKA independent of age. Higher reported insulin dose may represent lower endogenous insulin secretion with longer diabetes duration or insulin resistance due to puberty or obesity. In patients who miss insulin injections, higher recommended insulin dose may reflect futile efforts on the part of the clinician to control hyperglycemia. Among older children, in addition, underinsurance and the presence of psychiatric disorders were significant predictors of DKA. These factors can lead to poor compliance with diabetes treatment and to omissions of insulin injections, the most frequent cause of ketoacidosis.

Our study may have underestimated the effect of mental disorders, because eating disorders were excluded from the definition of psychiatric disorders. Eating disorders are frequent in children with diabetes and significantly affect patient care but may be difficult to identify.

The annual incidence of severe hypoglycemia in this study was 19 per 100 patient-years, similar to or higher than previously reported (Table 4). Some of the discrepancies can be explained by different definitions of severe hypoglycemia that investigators have used in the previous studies. A Joslin Clinic study used a definition similar to ours, but in a cohort of older children, aged 7 to 16 years, and found a lower rate of 8 per 100 patient-years. Consistent with previous reports, the highest incidence of hypoglycemia in our cohort was in the youngest children. In older children, it was still higher than that reported from the Joslin Clinic. However, our cohort included children with documented psychiatric disorders and unstable living conditions who are at higher risk for severe hypoglycemia but were excluded from the Joslin Clinic study. Male teenagers in our cohort had a severe hypoglycemia incidence rate (21 per 100 patient-years) similar to that in adolescents participating in the DCCT intensive treatment group (26.7 per 100 patient-years) while the rate in female teenagers (15 per 100 patient-years) was closer to that in the DCCT conventional treatment group (10 per 100 patient-years).

Somewhat different predictors anticipated severe hypoglycemia in pre-

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### Table 3. Incidence of Diabetic Ketoacidosis (DKA) in Children and Adolescents Before and After the Diabetes Control and Complications Trial

<table>
<thead>
<tr>
<th>Country</th>
<th>Study, y</th>
<th>Age Group, y</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Study Length</th>
<th>Definition of DKA</th>
<th>Incidence of DKA per 100 Person-Years</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>DCCT Group</td>
<td>13-17</td>
<td>195</td>
<td>Prospective</td>
<td>7.4 y</td>
<td>Blood glucose &lt;250 mg/dL, ketonuria, pH &lt;7.3, or bicarbonate &lt;15 mEq/L</td>
<td>4.7 Conventional therapy; 2.8 intensive therapy</td>
<td>...</td>
</tr>
<tr>
<td>Sweden</td>
<td>Nordfeldt and Ludvigsson</td>
<td>0-18</td>
<td>139</td>
<td>Prospective</td>
<td>3 y</td>
<td>Acidity</td>
<td>1.5</td>
<td>...</td>
</tr>
<tr>
<td>United States</td>
<td>Levine et al</td>
<td>2001</td>
<td>7-16</td>
<td>300</td>
<td>Prospective</td>
<td>DKA leading to ED visit or hospital admission</td>
<td>15</td>
<td>Higher HbA1c</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Smith et al</td>
<td>1998</td>
<td>1-17</td>
<td>Retrospective</td>
<td>6 y</td>
<td>pH &lt;7.3, or bicarbonate &lt;18 mEq/L</td>
<td>10</td>
<td>Female sex, family and school problems</td>
</tr>
<tr>
<td>Australia</td>
<td>Thornsett et al</td>
<td>1999</td>
<td>1-19</td>
<td>268</td>
<td>Retrospective</td>
<td>pH &lt;7.2, or bicarbonate &lt;10 mEq/L</td>
<td>12</td>
<td>...</td>
</tr>
<tr>
<td>United States</td>
<td>Current study</td>
<td>0-19</td>
<td>1243</td>
<td>Prospective</td>
<td>3.5 y</td>
<td>DKA leading to ED visit or hospital admission</td>
<td>8</td>
<td>Female sex, age, higher HbA1c, higher insulin dose, underinsurance, psychiatric disorders</td>
</tr>
</tbody>
</table>

*ED indicates emergency department; Hb, hemoglobin; and ellipses, not applicable. To convert blood glucose from mg/dL to mmol/L, multiply by 0.0555. ©2002 American Medical Association. All rights reserved.
pubertal vs older children. Duration of diabetes and underinsurance predicted severe hypoglycemia in both age groups. The increased risk of hypoglycemia with longer duration of diabetes is a well-known phenomenon.11,33 Underinsurance was our proxy for low socioeconomic status and unstable living conditions. Those factors could have a significant influence on a glycemic control and the rate of acute complications, as previously reported.23 On the other hand, studies from countries with nationalized health care systems have shown that socioeconomic status did not appear to play a major role in the risk of hypoglycemia.10,11

Among older children, lower HbA1c levels and the presence of psychiatric disorders were additional significant predictors of severe hypoglycemia. Beyond the first year of diabetes, HbA1c levels below 8% usually mark intensive insulin therapy and portend an increased risk for severe hypoglycemia.26 Psychiatric disorders, on the other hand, lead to severe hypoglycemia through less frequent blood glucose testing, and more chaotic diet and sleep and wake patterns.

In this study, we have confirmed that DKA and severe hypoglycemia are a recurrent problem in some children with diabetes. Recurrence appears to be related to age, duration of diabetes, blood glucose control, presence of psychiatric problems, and socioeconomic factors, which is in agreement with previous studies.3,31 The presence of previous episodes may help to identify patients at greater risk for developing acute complications.5,34

Acute complications in children with type 1 diabetes increase directly and indirectly the costs of care. Direct medical care charges associated with DKA episodes represent 28% of the direct medical care charges for all patients, and 56% for those with recurrent DKA.36 In 1997, the average charge per DKA episode was $6444. Assuming that the incidence rate of DKA in Denver applies to all estimated 150000 prevalent cases of type 1 diabetes patients younger than 20 years in the United States,37 the direct medical cost of DKA in this age group exceeds $77 million, annually. Using the incidence rate of severe hypoglycemia in Denver and the average annual cost of

### Table 4. Incidence of Severe Hypoglycemia in Children and Adolescents in the Era After the Diabetes Control and Complications Trial*

<table>
<thead>
<tr>
<th>Country</th>
<th>Study, y</th>
<th>Age Group, y</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Study Length</th>
<th>Definition of Hypoglycemia</th>
<th>Incidence of Hypoglycemia per 100 Person-Years</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>DCCT Research Group,21 1994</td>
<td>13-17</td>
<td>195</td>
<td>Prospective</td>
<td>7.4 y</td>
<td>Coma or seizure</td>
<td>10 Conventional therapy; 27 intensive therapy</td>
<td>...</td>
</tr>
<tr>
<td>Sweden</td>
<td>Nordfeldt and Ludvigsson,13 1997</td>
<td>1-18</td>
<td>146</td>
<td>Prospective</td>
<td>3 y</td>
<td>Coma or seizure</td>
<td>15-19 Lower HbA1c, higher insulin dose</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Davis et al,12 1998</td>
<td>0-18</td>
<td>709</td>
<td>Prospective</td>
<td>4 y</td>
<td>Coma or seizure</td>
<td>7.8 Younger age, lower HbA1c</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Levine et al,6 2001</td>
<td>7-16</td>
<td>300</td>
<td>Prospective</td>
<td>1 y</td>
<td>Coma, seizure, glucagon injection, or dextrose intravenously</td>
<td>8 Higher HbA1c</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Allen et al,4 2001</td>
<td>0-29</td>
<td>415</td>
<td>Prospective</td>
<td>2.5 y</td>
<td>Coma during an insulin reaction</td>
<td>... Lower HbA1c, older age, underinsurance</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Tupola et al,22 1998</td>
<td>1-24</td>
<td>287</td>
<td>Prospective Retrospective</td>
<td>2 y</td>
<td>Coma, seizure, or glucagon injection</td>
<td>3.1 Lower HbA1c, higher insulin dose</td>
<td>3.6</td>
</tr>
<tr>
<td>United States</td>
<td>Lteif et al,7 2001</td>
<td>0-9</td>
<td>59</td>
<td>Retrospective</td>
<td>2 y</td>
<td>Coma or seizure</td>
<td>5-66 Younger age</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Thomsett et al,29 1999</td>
<td>1-19</td>
<td>268</td>
<td>Retrospective</td>
<td>3 mo</td>
<td>Coma or seizure</td>
<td>25 Age, lower HbA1c, No. of visits</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Mortensen,32 1997</td>
<td>1-18</td>
<td>2873</td>
<td>Cross-sectional</td>
<td>5 mo</td>
<td>Coma or seizure</td>
<td>22 Younger age or lower HbA1c</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Rosilio et al,11 1998</td>
<td>1-19</td>
<td>2579</td>
<td>Cross-sectional</td>
<td>6 mo</td>
<td>Coma, seizure, or glucagon injection</td>
<td>45 Lower HbA1c, more exercise, No. of blood glucose measurements per day</td>
<td></td>
</tr>
<tr>
<td>Canada, Europe, Japan</td>
<td>Danne et al,32 2001</td>
<td>0-18</td>
<td>2780</td>
<td>Cross-sectional</td>
<td>5-6 mo</td>
<td>Coma or seizure</td>
<td>7-20 Poor glycemic control</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Current study</td>
<td>0-19</td>
<td>1243</td>
<td>Prospective</td>
<td>3.5 y</td>
<td>Coma, seizure or admission</td>
<td>19 Male sex, younger age, lower HbA1c, higher insulin dose, underinsurance, psychiatric disorders</td>
<td></td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable.
Those underinsured, with psychiatric per 100 patient-years) and severe hypo-
glycemia in US children is estimated at $174 per person.25 the direct medical cost for severe hypo-
glycemia in US children is $26 million. Thus the combined di-
rect medical care charges for DKA and severe hypo-
glycemia in US children with diabetes probably exceeded $100 million per year during the late 1990s. Further studies are needed to update these figures and to estimate, in addi-
tion, indirect cost (eg, lost productivity and diminished quality of life).

Although death or cerebral edema ap-
pear to be uncommon outcomes of acute diabetic complications in our population with easy access to special-
ized care (we found no death and only 2 cases of documented cerebral edema in the study cohort), these are much more likely among patients with geo-
graphic or financial barriers to care.37

Intervention programs that im-
prove glycemic control have been shown to reduce the risk for DKA and severe hypo-
glycemia and medical charges for these complications.38 How-
ever, there is a paucity of efficacy data concerning additional medical and psy-
chosocial support interventions to im-
prove outcomes in children at risk. Our data suggest that aggressive treatment of psychiatric disorders and improved socioeconomic status (including bet-
ter insurance coverage for and access to diabetes care) should be strongly consid-
ered.

In conclusion, US children with type 1 diabetes are at high risk for DKA (8 per 100 patient-years) and severe hypo-
glycemia (19 per 100 patient-years). Those underinsured, with psychiatric disorders, or at the extremes of HbA1c distribution should be targeted for in-
terventions aimed at these modifiable risk factors.

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tellectual content: A. Rewers, Chase, Mackenzie, Walraens, Roback, M. Rewers, Hamman, Klingensmith.


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