Trends in the Prevalence of Ketoacidosis at Diabetes Diagnosis: The SEARCH for Diabetes in Youth Study

WHAT'S KNOWN ON THIS SUBJECT: Diabetic ketoacidosis (DKA) is a life-threatening condition and often the presenting symptom of newly diagnosed type 1 or type 2 diabetes in youth. SEARCH previously reported that the prevalence of DKA at diagnosis was 25.5% in 2002–2003.

WHAT THIS STUDY ADDS: DKA in youth with type 1 diabetes remains a problem, with almost one-third presenting with DKA. Among youth with type 2 diabetes, DKA was less common and decreased by ∼10% per year, suggesting improved detection or earlier diagnosis.

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abstract

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OBJECTIVE: To estimate temporal changes in the prevalence of diabetic ketoacidosis (DKA) at diagnosis of type 1 or type 2 diabetes in youth and to explore factors associated with its occurrence.

METHODS: Five centers identified incident cases of diabetes among youth aged 0 to 19 years starting in 2002. DKA presence was defined as a bicarbonate level <15 mmol/L and/or a pH <7.25 (venous) or <7.30 (arterial or capillary) or mention of DKA in the medical records. We assessed trends in the prevalence of DKA over 3 time periods (2002–2003, 2004–2005, and 2008–2010). Logistic regression was used to determine factors associated with DKA.

RESULTS: In youth with type 1 diabetes ($n = 5615$), the prevalence of DKA was high and stable over time (30.2% in 2002–2003, 29.1% in 2004–2005, and 31.1% in 2008–2010; P for trend = .42). Higher prevalence was associated with younger age at diagnosis ($P < .0001$), minority race/ethnicity ($P = .019$), income ($P = .019$), and lack of private health insurance ($P = 008$). Among youth with type 2 diabetes ($n = 1425$), DKA prevalence decreased from 11.7% in 2002–2003 to 5.7% in 2008–2010 (P for trend = .005). Higher prevalence was associated with younger age at diagnosis ($P = .001$), minority race/ethnicity ($P = .013$), and male gender ($P = .001$).

CONCLUSIONS: The frequency of DKA in youth with type 1 diabetes, although stable, remains high, indicating a persistent need for increased awareness of signs and symptoms of diabetes and better access to health care. In youth with type 2 diabetes, DKA at onset is less common and is decreasing over time. *Pediatrics* 2014;133:e938–e945

The SEARCH for Diabetes in Youth Study has estimated that there were at least 188 811 youth with diabetes in the United States in 2009: 168 141 with type 1 diabetes and 19 147 with type 2 diabetes.[1] In the United States[2] and worldwide,[3] the incidence of type 1 diabetes in youth has been increasing by 3% to 4% per year, with limited estimates for type 2 diabetes except in minority populations in whom increased prevalence has also been reported.[4] Diabetic ketoacidosis (DKA) due to insulin deficiency can be a life-threatening condition, and is often the presenting symptom of new-onset cases in both type 1 and type 2 diabetes.[5] It has been reported to be present in 25% to 30% of type 1 diabetes cases at onset[6–10] and from 4% to 29% in youth with type 2 diabetes, depending on race/ethnicity.[10–14] SEARCH previously reported that the prevalence of DKA at diagnosis was 25.5% in 2002–2003.[10]

It is not known whether the presence of DKA at diagnosis has changed over time. It has been decreasing in Sweden[15] and Finland[16,17] from the late 1970s to the mid-2000s, coincident with programs aimed at increasing DKA awareness. However, no such trends were reported from Austria or Germany.[18–20] There is limited long-term trend information in youth with type 1 diabetes from North American populations,[21–23] and to our knowledge, no trend data on DKA among youth with type 2 diabetes. Thus, the goal of this analysis was to estimate temporal changes in the prevalence of DKA at diabetes onset among youth aged 0 to 19 years when diagnosed with type 1 or type 2 diabetes, overall and by age, gender, and race/ethnicity, and to explore factors associated with its occurrence over time.

METHODS

Data for this analysis derive from the registry component of the SEARCH for Diabetes in Youth Study. The study protocol was reviewed and approved by the local institutional review boards that had jurisdiction. All centers complied with the privacy requirements of the Health Insurance Portability and Accountability Act. Because the SEARCH registry attempts to identify 100% of all cases, case identification was conducted with an approved Health Insurance Portability and Accountability Act consent waiver at most locations. Written informed consent/assent for a study visit was obtained according to the local institutional review board requirements.

A detailed description of the SEARCH methods has been published.[24,25] In brief, SEARCH is an ongoing multicenter study that, in 2002, began population-based ascertainment of incident cases of diabetes in youth aged 0 to 19 years of age. Cases are identified as follows: (1) in geographically defined populations in the states of Ohio, Washington, South Carolina, and Colorado; (2) among health plan enrollees in Kaiser Permanente Southern California; and (3) coordinated by the Colorado site, among Indian Health Service beneficiaries in American Indian populations in Arizona and New Mexico. Active surveillance systems were based on networks of pediatric and adult endocrinologists, existing pediatric diabetes databases, hospitals, clinical databases and electronic health records, and other health care providers. All case reports were validated on the basis of physician reports or medical record review and only validated and eligible cases were included. Case reports were registered anonymously with the coordinating center at Wake Forest School of Medicine (Winston-Salem, NC).

Persons with diabetes ≥18 years of age identified by the SEARCH recruiting network and parents of youth <18 years were asked to complete an initial survey that included their age at diagnosis, treatment history, race or ethnicity, insurance, and parental education. Medical records for the period from diagnosis to 6 months after diagnosis were reviewed to collect information on the prevalence of DKA at diagnosis. This protocol was conducted for all registered cases under a waiver of written informed consent from most participating institutions. This report covers 3 intervals spanning a 9-year time period from 2002 to 2010 (2002–2003, 2004–2005, and 2008–2010), because information to assess the presence of DKA was not collected for the cohorts diagnosed in 2006 and 2007. Methods used over time were identical in each interval. The availability of medical record data to assess DKA was somewhat higher for youth with type 1 diabetes (on average, 22% missing records, improving over time from 26% to 19%) than for youth with type 2 diabetes (on average, 26% missing records, improving over time from 39% to 14%). This situation was due to variation in institutional review board practices at participating institutions and hospitals, both within and across sites, in granting permission to review medical records under a waiver of written informed consent. All trend analyses included only youth with available medical record data. Because information about insurance, income, and parental education was inconsistently available in the medical records, the associations between these factors and DKA at diagnosis were examined only in the subset of participants for whom both medical records and survey data were available.

Definitions of Variables

DKA was considered to be present if, in the context of hyperglycemia, any of the following were present: a blood

bicarbonate level <15 mmol/L, and/or a pH < 7.25 (venous) or <7.30 (arterial or capillary), and/or a DKA diagnosis mentioned in the medical records.[10]

Data on race and ethnicity were based on self-reports or medical records. On the basis of 2000 US Census classification, participants were categorized as Hispanic, African-American, Asian or Pacific Islander, American Indian, non-Hispanic white, and multiple, other, or unknown race. Classification of diabetes type was determined on the basis of the clinical diagnosis made by a health care provider and was collected from the providers at the time of the case report to SEARCH or abstracted from medical records. The clinical type was categorized as type 1 (including 1A, 1B), type 2, or other or unknown diabetes type. Clinical diabetes type was previously shown to be consistent with an etiologic classification of diabetes type on the basis of autoimmunity and insulin resistance, as assessed by the SEARCH study.[26] Family income, highest parental education, and type of health insurance were obtained through the health questionnaire or initial participant survey. Responses to questions about health insurance sources, which allowed multiple choices, were categorized hierarchically as "private," which included private only and private plus anything else, and "other/none," which included Medicaid only, Indian Health Service only, other types of insurance, and none. Parental educational attainment is that of the parent with the higher attainment.

Overall, there were 9213 youth aged 0 to 19 years diagnosed with type 1 or type 2 diabetes and registered in 2002–2003, 2004–2005, and 2008–2010. We excluded 2099 (23%) incident cases due to missing medical records and another 74 cases of type 2 diabetes aged <10 years, leaving 7040 youth for this analysis (5615 with type 1 diabetes

aged 0–19 years and 1425 with type 2 diabetes aged 10–19 years).

Statistical Analysis

Statistical analyses were performed by using SAS 9.3 (SAS Institute, Cary, NC). The period prevalence of DKA at diagnosis (per 100 youth with type 1 or type 2 diabetes) was calculated, along with 95% confidence intervals (CIs), by age group, gender, and race/ethnicity. Poisson regression was used to test for change over time within each stratum of interest. Multivariable logistic regression analyses were used to identify factors associated with DKA at diagnosis over time. In these models, time was treated as a continuous/ordinal variable to examine whether there was a linear trend, and specifically to take into account the unequal spacing between time categories. All of the tests were 2-sided, and a P value <.05 was considered statistically significant.

RESULTS

There were 7040 youth with new-onset diabetes available for this analysis: 5615 had type 1 and 1425 had type 2 diabetes. Table 1 shows the prevalence of DKA by type of diabetes, time period, and age group.

Type 1 Diabetes

Among youth with type 1 diabetes, the prevalence did not significantly change over time, with a prevalence of 30.2% (95% CI: 27.8%–32.5%) in 2002–2003, 29.1% (95% CI: 26.9%–31.4%) in 2004–2005, and 31.1% (95% CI: 29.3%–32.9%) in 2008–2010 (P for trend = .42). The overall prevalence was highest in the 0- to 4-year age group (~39%) and lowest in the 15- to 19-year age group (~23%) . No changes over time in DKA at onset were observed within each age group.

Figure 1 A and B shows the changes over time in the prevalence of DKA at diagnosis in youth with type 1 diabetes by gender and race/ethnicity, respectively. Rates were similar in boys and girls but higher in Hispanic and African-American youth than among non-Hispanic white youth. Due to small numbers we were unable to explore trends in Asian Pacific Islander or American Indian youth. However, there were no statistically significant gender- or race/ethnicity-specific changes over time.

We used logistic regression to explore whether our findings were influenced by adjustment for sociodemographic factors and to determine whether such factors were associated with DKA at diagnosis. Table 2 shows that, after adjustment, there were no significant changes over time in DKA at onset of type 1 diabetes. However, across the entire time period, younger youth had a significantly higher prevalence of DKA than those diagnosed at older ages. Similarly, nonwhite youth had a higher prevalence than did non-Hispanic whites, as did those without private insurance (by 22% and 31%, respectively). Household income showed a significant association with DKA, where households in the $25 000 to $49 000 range had significantly higher odds of DKA than did those in the $50 000 to $74 000 range. Gender and parental education were not significantly independently associated with DKA among youth with type 1 diabetes.

Type 2 Diabetes

Table 1 also shows the trends for youth with type 2 diabetes aged 10 to 19 years, because there were too few under the age of 10 to estimate rates of DKA in each period. The prevalence decreased from 11.7% (95% CI: 8.2%–15.2%) in 2002–2003 to 6.3% (95% CI: 3.7%–8.9%) in 2004–2005 and 5.7% (95% CI: 4.1%–7.4%) in 2008–2010 (P for trend = .005). DKA at onset was

TABLE 1 Changes Over Time in Prevalence of DKA at Diagnosis by Type of Diabetes and Age Group: The SEARCH for Diabetes in Youth Study (2002–2003, 2004–2005, and 2008–2010) Incident Cases

Incident year	0–4 Years			5–9 Years			10–14 Years			15–19 Years			All		
	n	Prevalence per 100 cases, %	95% CI	n	Prevalence per 100 cases, %	95% CI	n	Prevalence per 100 cases, %	95% CI	n	Prevalence per 100 cases, %	95% CI	n	Prevalence per 100 cases, %	95% CI
Type 1 diabetes															
2002–2003	121	40.1	34.5–45.6	127	27.9	23.8–32.0	153	28.9	25.1–32.8	41	22.9	16.8–29.1	442	30.2	27.8–32.5
2004–2005	98	36.2	30.4–41.9	126	25.2	21.4–29.0	186	31.5	27.8–35.3	46	22.4	16.7–28.2	456	29.1	26.9–31.4
2008–2010	175	41.1	36.4–45.8	247	29.8	26.7–32.9	286	30.9	27.9–33.9	95	23.5	19.4–27.7	803	31.1	29.3–32.9
P for trend		.62			.29			.65			.83			.42	
Type 2 diabetes															
2002–2003		—	—		—	—	22	14.7	9.0–20.3	16	9.2	4.9–13.5	38	11.7	8.2–15.2
2004–2005		—	—		—	—	16	9.5	5.1–14.0	5	3.1	0.4–5.7	21	6.3	3.7–8.9
2008–2010		—	—		—	—	28	7.3	4.7–9.9	16	4.2	2.2–6.2	44	5.7	4.1–7.4
P for trend								.02			.08			.005	

Cases with missing medical record data were excluded from these analyses.

more common among youth aged 10 to 14 years than in 15- to19-year-old youth, and changes over time were somewhat more pronounced in the younger group (P for trend = .02 vs .08 in the older group). There were too few cases with type 2 diabetes to stratify by gender or race/ethnic group. In multivariate logistic regression analyses, among youth with type 2 diabetes, there was an ~10% per year decrease in DKA prevalence after adjustment for sociodemographic factors (odds ratio = 0.90, P = .004). Younger onset age, minority race/ethnicity, and male gender had significantly higher DKA prevalence. Due to very small numbers and missing data, we were not able to explore the role of parental education, health insurance, or household income in youth with type 2 diabetes.

In addition to fitting a model that treated year as an ordinal variable, we also examined year as a categorical variable. We found similar results for type 1 and 2 diabetes patients as seen with the ordinal variable parameterization; however, there was some evidence that the change in prevalence of DKA over time for type 2 diabetes participants was stronger in the early years (2002–2003 and 2004–2005) than in the later years (2004–2005 vs 2008–2010).

DISCUSSION

We have shown that the prevalence of DKA at diagnosis of diabetes, a life-threatening but potentially preventable condition, remains an important problem. The frequency of DKA in youth with type 1 diabetes appears to be stable but remains high, with almost one-third of all youth with type 1 diabetes presenting with DKA, suggesting a persistent need for increased awareness of signs and symptoms of diabetes and better access to health care. In contrast, among youth with type
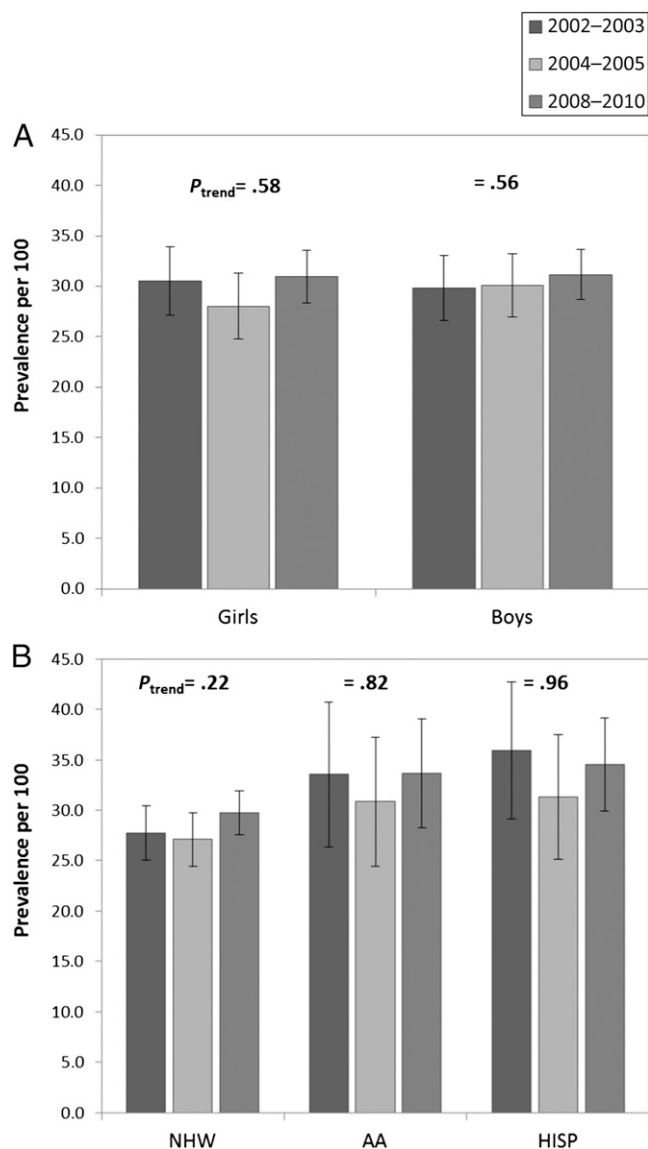
FIGURE 1
A, Prevalence of DKA at diagnosis of type 1 diabetes by gender. B, Prevalence of DKA at diagnosis of type 1 diabetes by race/ethnicity and year. AA, African-American; HISP, Hispanic; NHW, non-Hispanic white.

2 diabetes, DKA was less common and decreased by ~10% per year, suggesting improved detection of symptoms or diagnosis earlier in the clinical course.

Type 1 Diabetes

The rates of DKA among youth with type 1 diabetes were similar to the 29% prevalence reported in Colorado for the period 1998–2001[21] and the 28% prevalence from a single center in

Denver, Colorado,[27] in 2002–2003.[10] A previous report from the Colorado IDDM (insulin-dependent diabetes mellitus) Registry reported a higher prevalence of 38% in 1978–1982, suggesting that a longer period of observation may identify decreasing DKA trends among youth with type 1 diabetes.

The DKA prevalence among type 1 youth with onset at <15 years was 33% in the 24 centers in the Eurodiab Study

in 1989–1994.[28] In Sweden, the prevalence ranged from 9% to 14% across ages 0 to 5 to 11 to 15 years at onset in 1997–2001.[15] DKA prevalence in northern Finland was also somewhat lower than we report, at 18.9% in 1992–2001.[17] In both of these areas, declines in DKA were seen from earlier periods. However, in Germany, among >14 000 youth from 106 centers, the prevalence was 21.1%,[20] with no decrease over time, which was consistent with our findings. A lack of decline in DKA at presentation was also reported from Austria (1989–2008), although the prevalence of DKA was higher than in SEARCH (37.2% at onset).[19]

Similar to our data, a systematic review of 46 studies involving >24 000 children in 31 countries worldwide identified younger age, ethnic minority, and lack of health insurance, among others, as major risk factors for DKA at onset with type 1 diabetes.[29] Younger age was consistently associated with increased risk of DKA at onset in numerous studies, and the reasons are likely multifactorial.[29] Toddlers are less likely to verbalize symptoms and early symptom recognition is more difficult in young children, leading to delayed diagnosis and treatment. On the other hand, young children may experience more aggressive and faster metabolic deterioration.[15] The Environmental Determinants of Diabetes in the Young (TEDDY) Study recently found that DKA prevalence in youth <5 years of age who were followed regularly and educated about diabetes in the TEDDY study was lower than among registry youth who were not under follow-up, suggesting that parental education, closer monitoring of signs and symptoms of diabetes, and knowledge of being at high risk of type 1 diabetes can result in lower DKA prevalence at onset of diabetes.[30] Finally, our findings of a higher prevalence of DKA in minority youth with type 1 diabetes, youth without

TABLE 2 Correlates of DKA by Type of Diabetes: The SEARCH for Diabetes in Youth Study (2002–2003, 2004–2005, and 2008–2010) Incident Cases

	Odds Ratio	95% CI
Type 1 diabetes (n = 3706)		
Time (per 1 year)	1.013	0.988–1.039
Onset age		
5–9 vs 0–4 years	0.577	0.474–0.704
10–14 vs 0–4 years	0.729	0.602–0.882
15–19 vs 0–4 years	0.389	0.293–0.518
Race: Nonwhite versus NHW	1.218	1.033–1.436
Insurance: other/none versus private	1.312	1.075–1.602
Income		
<$25 000 vs $50 000–$75 000	1.162	0.872–1.548
$25 000–49 vs $50 000–$75 000	1.339	1.066–1.683
≥$75 000 vs $50 000–$75 000	0.951	0.771–1.173
Refused versus $50 000–$75 000	1.115	0.822–1.513
Type 2 diabetes (n = 1388)		
Time (per 1 year)	0.904	0.843–0.969
Onset age: 15–19 vs 10–14 years	0.500	0.327–0.765
Race: Non-white versus NHW	2.204	1.183–4.105
Gender: female versus male	0.505	0.334–0.762

Cases with missing medical record data were excluded from these analyses. NHW, non-Hispanic white.

private insurance, and those with lower family income are consistent with previous US reports[31] and suggest a persistent need for improved health care access.

Type 2 Diabetes

Among youth with type 2 diabetes, information on the occurrence of DKA at onset is limited, and our study is the first, to our knowledge, to report on potential changes over time. Estimates of DKA prevalence at onset with type 2 diabetes vary substantially, from 41.4% and 16% among African-American youth in Cincinnati[14] and Arkansas, respectively,[13] to 8% among African Canadians and Southeast Asians in Toronto,[11] and 4.2% among Canadian Aboriginal youth.[12] We found that a higher prevalence of DKA was associated with younger age, minority race/ethnicity, and male gender. Whereas we do not have a direct explanation for the observed decreasing trend over time, possible explanations include improved access to care (although adjustment for minority racial/ethnic group did not account for changes in DKA prevalence) and/or improved diagnosis in at-risk individuals

(although we were not able to document significant differences in hemoglobin A1c levels over time among youth who had a baseline study visit: mean (SD) levels in the 3 periods were 7.54% (2.31%), 7.18% (2.03%), and 7.55% (2.06%), respectively. In addition, future years of data may be useful to examine whether the observed changes in DKA prevalence in youth with type 2 diabetes are leveling off or not.

Limitations and Strengths

Our study has some limitations. The period of assessment was only 9 years, which may have limited our ability to detect small changes in DKA prevalence in specific racial/ethnic groups. The availability of medical records to assess the presence of DKA was not complete, and cases with missing records were excluded. However, in youth with type 1 diabetes, we found no major differences between demographic characteristics of youth with and without medical record data available. In contrast, in youth with type 2 diabetes, the proportion with missing records declined substantially over time, and minority youth were more

likely than non-Hispanic white youth to have missing medical record data in each time period. Because minority youth had a higher DKA prevalence, this finding may have underestimated the observed decrease in DKA prevalence over time in youth with type 2 diabetes. We used a provider assessment of diabetes type for these analyses, which is especially problematic in youth with type 2 diabetes. However, we have previously shown good agreement between provider assessment of diabetes type and etiologic diabetes type.[26] Also, our finding of a decreasing prevalence of DKA in youth with type 2 diabetes over time was maintained after excluding a small number of participants with type 2 diabetes and positive auto-antibodies. Strengths of the study include the population-based design with consistent definitions of DKA over time, the largest and most diverse US sample of youth with type 1 diabetes, and the first report of changes over time in DKA in type 2 diabetes in youth.

CONCLUSIONS

We found no evidence that DKA at diabetes onset among youth with type 1 diabetes has been changing over time in centers located in multiple geographic areas in the United States. Across the study period, a higher DKA prevalence was independently associated with younger onset age, minority race/ethnicity, lower family income, and lack of private insurance. Although stable, the prevalence of DKA remains high among US children at diagnosis with type 1 diabetes, indicating a continuing need for increased awareness of the signs and symptoms of type 1 diabetes and better access to health care. In youth with type 2 diabetes, DKA at onset is less common and seems to be decreasing over time,

suggesting improved diagnosis in at-risk individuals. With changes in the availability of health insurance and associated health care access on the horizon, it may be possible to begin reducing DKA rates in the near future, although it is likely that additional outreach to minority populations will be needed to decrease DKA in these groups.

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