Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control

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Diabetes Care 2017;40:1249–1255 | https://doi.org/10.2337/dc17-0558

OBJECTIVE

This study tested the hypothesis that diabetic ketoacidosis (DKA) at diagnosis of type 1 diabetes in children predicts poor long-term glycemic control independently of established risk factors.

RESEARCH DESIGN AND METHODS

This was a prospective cohort study of 3,364 Colorado residents diagnosed with type 1 diabetes before 18 years of age, in 1998–2012, and monitored for up to 15 years. Of those, 1,297 (39%) had DKA at diagnosis (blood glucose >250 mg/dL, and venous pH <7.3 or bicarbonate <15 mEq/L). Severity of DKA was further classified as mild/moderate (pH 7.10–7.29 or bicarbonate 5–14 mEq/L) or severe (pH <7.10 or bicarbonate <5 mEq/L). HbA_{1c} levels were measured an average of 2.8 times/year (median 20 HbA_{1c} values/patient). A linear mixed model was used to examine the effect of DKA on long-term HbA_{1c} levels, adjusting for age, race/ethnicity, sex, family history of diabetes, health insurance, and insulin pump use.

RESULTS

DKA at diagnosis predicted persistently elevated HbA_{1c} levels. Compared with children without DKA, HbA_{1c} tracked 1.4% (15.3 mmol/mol) higher in those with severe DKA ($P < 0.0001$) and 0.9% (9.8 mmol/mol) higher in those with mild/moderate DKA at diagnosis ($P < 0.0001$). These effects were independent of ethnic minority status or lack of health insurance at diagnosis that predicted higher HbA_{1c} by 0.5% (5.5 mmol/mol; $P < 0.0001$) and 0.2% (2.2 mmol/mol; $P < 0.0001$), respectively. Insulin pump use or having a parent or sibling with type 1 diabetes predicted lower long-term HbA_{1c} by, respectively, 0.4% (4.4 mmol/mol; $P < 0.0001$) and 0.2% (2.2 mmol/mol; $P = 0.01$).

CONCLUSIONS

DKA at diagnosis of type 1 diabetes in children predicts poor long-term glycemic control, independent of demographic and socioeconomic factors.

Diabetic ketoacidosis (DKA) is a life-threatening complication affecting 30–46% of children with newly diagnosed type 1 diabetes in the U.S. (1,2). Although mortality is currently <1%, DKA is still associated with detrimental neurocognitive outcomes (3,4). DKA is largely preventable because it often results from delayed care caused by low awareness of diabetic symptoms in the community and among health care providers (5–7).

Type 1 diabetes results from the autoimmune destruction of β-cells in the pancreas and the subsequent lack of insulin. Severe hyperglycemia and systemic inflammation associated with DKA have been shown to further deplete functional pancreatic islets (8).

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Received 18 March 2017 and accepted 5 June 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0558/-/DC1.

Lower residual β-cell function (9), higher insulin requirements (10), and worse glycemic control (11) during the following 1–2 years have been shown in children with DKA at presentation compared with those diagnosed with milder symptoms. Early tight glycemic control, as measured by hemoglobin A_{1c} (HbA_{1c}), prevents diabetic complications (12–14), while loss of residual β-cell function increases the risk of retinopathy, nephropathy, neuropathy, and severe hypoglycemia (15). DKA may worsen glycemic control and prognosis of diabetes through exacerbation of β-cell loss at diagnosis independently of other factors such as age and intensity of postdiagnosis management.

Despite advances in medical management, type 1 diabetes remains a burdensome disease with everyday challenges and substantial medical costs. In addition, most youth with type 1 diabetes do not meet the American Diabetes Association guidelines for glycemic control (16) and are likely to experience excess morbidity and premature mortality (17–19).The objective of this study was to test the hypothesis that children who present in DKA at the diagnosis of type 1 diabetes experience worse glycemic control later in the course of the disease, independently of demographic and socioeconomic factors or access to care that are associated with both onset DKA and long-term diabetes care and glycemic control. If confirmed as an independent predictor of glycemic control, DKA should be seen as a preventable risk factor for long-term diabetic complications.

RESEARCH DESIGN AND METHODS

Study Population

The study cohort consists of 3,364 Colorado residents aged 0–17 years diagnosed with type 1 diabetes between 1998 and 2012 and monitored at the Barbara Davis Center for Diabetes (BDC) for at least 1 year and up to 17 years, until 8 April 2016. Type 1 diabetes was diagnosed by a physician based on the clinical phenotype and measurement of islet autoantibodies. Of the 3,926 potential study participants, excluded were children with type 2 diabetes (n = 238), monogenic diabetes (n = 13), diabetes secondary to cystic fibrosis (n = 72) or other conditions (n = 40), and indeterminate diabetes (n = 19) (2). Also excluded were children with unknown DKA status at diagnosis (n = 105) and those for whom fewer than two HbA_{1c} measurements were available (n = 75). These exclusions left 3,364 children with type 1 diabetes for the study population of interest.

Demographic, insurance status, and clinical characteristic data were extracted from medical records. Patients were monitored at the BDC, which serves youth with diabetes in Colorado. The BDC is the default ambulatory service for the Children's Hospital of Colorado Network of Care (CHCO), which provides more than 60% of general pediatric care and more than 90% of pediatric subspecialty care in Colorado. A population-based registry of childhood diabetes, Search for Diabetes in Youth (SEARCH), has shown that 82% of all Colorado children with diabetes and 84% of those with type 1 diabetes diagnosed between 2002 and 2012 were seen at the BDC. This pattern has not changed during the past 15 years; thus, the data presented in this analysis are representative of the state of Colorado.

Race/ethnicity was based on parental report defined using the 2000 U.S. Census. Because only 16% of our participants were Hispanic, 4% non-Hispanic Black, and 4% other, these race categories were combined, and subsequently in the analyses race was dichotomized into non-Hispanic white versus other (nonwhite or Hispanic). Insurance status before diagnosis of diabetes was categorized as *1*) private insurance, *2*) government-provided insurance (Medicaid, TRICARE, Colorado Resident Discount Program, or Child Health Plan Plus), or *3*) none. HbA_{1c} levels were measured at baseline and also at each visit (2.8 visits/year, on average; median 20 visits/patient) using the DCA 2000+ (Bayer).

Standard criteria (20) were used to define DKA (blood glucose >250 mg/dL, and venous pH <7.3 or bicarbonate <15 mEq/L). Severity of DKA was further classified as mild/moderate (pH 7.10–7.29 or bicarbonate 5–14 mEq/L) or severe (pH <7.10 or bicarbonate <5 mEq/L). The Colorado Institutional Review Board (COMIRB) approved the protocol and granted a waiver of informed consent.

Statistical Analysis

A Student t test was used to compare continuous variables at baseline between the children who presented with DKA and those without DKA. A χ^2 test was used to compare categorical data. Individual average HbA_{1c} levels were calculated annually, starting 60 days after the diagnosis through the follow-up. Pearson correlation coefficients were used to examine the correlation and covariance matrices for the repeated measures of HbA_{1c} level over time.

A linear mixed model was used to estimate the mean change in the HbA_{1c} levels over time by DKA status (yes/no) to account for the inherent correlation of repeated measures on the same individual over time. The first model was unadjusted, and the fixed effect of the model consisted of time (yearly), DKA status (yes/no), and an interaction of DKA status by time. A second unadjusted linear mixed model was used to estimate the mean change in the HbA_{1c} level over time by DKA severity (no, mild/moderate, severe). A final linear mixed model was used to estimate the mean change in the HbA_{1c} level over time by DKA severity category (no, mild/moderate, severe), adjusting for age at diagnosis, race/ethnicity, sex, family history of diabetes, insurance status, and insulin pump use.

For all linear mixed models performed, model assumptions, such as a normally distributed outcome measure, were checked. All models were further assessed to verify there was in fact a linear trend over time and that a quadratic or spline term did not significantly improve the model fit. Finally, transformed residuals, using the Cholesky decomposition technique, were examined to assess the adequacy of the fitted models and additionally to look for an indication of any outliers. Because the mixed model analyses assume data are missing at random, the missing data pattern was checked, and the assumption was verified by plotting the means over time stratified by the time of the last measure completed. A P value of <0.05 was considered statistically significant for all analyses. The statistical analysis was performed using SAS 9.3 software of the SAS System for Windows.

RESULTS

DKA at diagnosis was present in 1,297 of the study participants (38.6%). The baseline characteristics of the study population stratified by DKA status are reported in Table 1. Children who presented in DKA were younger, more often nonwhite

Table 1—Baseline characteristics of the study population

Variable	Missing *n* (%)	DKA *n* = 1,297	No DKA *n* = 2,067	*P* value
Age at onset (years)*	0 (0)	8.8 ± 4.6	9.4 ± 4.3	<0.0001
Sex	0 (0)			0.16
Female		585 (45.1)	956 (46.2)	
Male		712 (54.9)	1,111 (53.8)	
Ethnicity	4 (0.1)			<0.0001
Non-Hispanic white		897 (69.3)	1,638 (79.3)	
Nonwhite or Hispanic		398 (30.7)	427 (20.7)	
Insurance status	22 (0.7)			<0.0001
Private		743 (57.9)	1,535 (74.6)	
Government		390 (30.4)	401 (19.5)	
None		151 (11.7)	122 (5.9)	
Location of residence	0 (0)			0.11
Rural		122 (9.4)	189 (9.2)	
Urban		440 (33.9)	633 (30.6)	
Metropolitan		735 (56.7)	1,245 (60.2)	
Family history	43 (1.3)			<0.0001
First-degree relative with diabetes		58 (4.5)	287 (14.0)	
Family history of diabetes				
Yes		576 (45.3)	879 (42.9)	
No		638 (50.2)	883 (43.1)	
Insulin pump use	0 (0)	471 (36.3)	844 (40.8)	0.009
At type 1 diabetes diagnosis*	410 (12)			
HbA_{1c} (%)		12.1 ± 2.0	10.8 ± 2.5	<0.0001
HbA_{1c} (mmol/mol)		109 ± 21.9	95 ± 27.3	
At 60 days post type 1 diabetes diagnosis*	278 (8.3)			
HbA_{1c} (%)		8.4 ± 1.7	8.0 ± 1.5	<0.0001
HbA_{1c} (mmol/mol)		68 ± 18.6	65 ± 16.4	
DKA severity	256/1,297 (19.7)			—
Mild or moderate		693 (66.6)	—	
Severe		348 (33.4)	—	

*Student *t* test was used to compare continuous variables, which are presented as mean ± SD; otherwise, a χ^2 test was used to compare categorical data, which are presented as *n* (%).

or Hispanic, more often uninsured or covered by a government-provided insurance plan, and less likely to have first-degree relatives with type 1 diabetes than children presenting without DKA. As expected, HbA_{1c} levels at diagnosis of type 1 diabetes, as well as 60 days after the diagnosis, were higher in children diagnosed in DKA. Among children who presented in DKA, one-third had severe DKA.

Longitudinal HbA_{1c} levels up to 15 years after type 1 diabetes diagnosis are shown by DKA status in Fig. 1 and by severity of DKA in Fig. 2. Throughout the entire study period, HbA_{1c} levels in children presenting in DKA remained 0.3–1.0% (3.3–10.9 mmol/mol) higher than those diagnosed with milder symptoms. There was an apparent dose-response relationship between the severity of DKA and the average HbA_{1c} during the entire follow-up period. HbA_{1c} gradually increased in all groups, consistent with gradual loss of endogenous insulin secretion reported both in type 1 and type 2 diabetes.

Multivariate Analysis

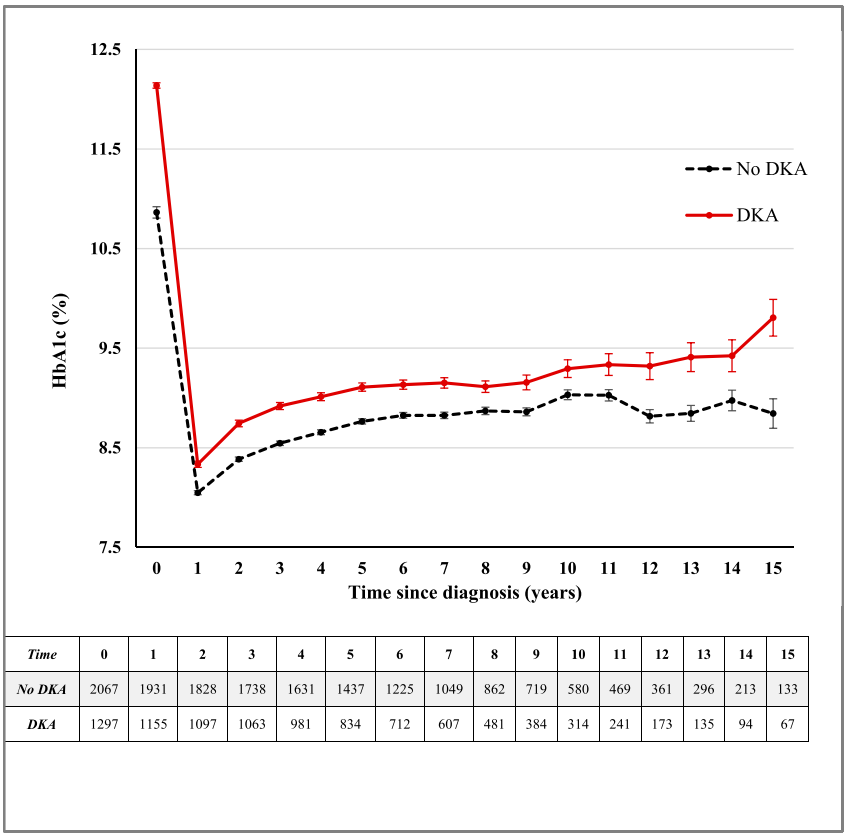
DKA at diagnosis predicted elevated longitudinal HbA_{1c} levels independent of other factors in a multivariate mixed-effects model (Table 2). Compared with children without DKA, HbA_{1c} tracked 1.4% (15.3 mmol/mol) higher in those with severe DKA ($P < 0.0001$) and 0.9% (9.8 mmol/mol) higher in those with mild/moderate DKA ($P < 0.0001$). These effects were independent of ethnic minority status or lack of health insurance at diagnosis, which predicted higher HbA_{1c} by 0.5% (5.5 mmol/mol; $P < 0.0001$) and 0.2% (2.2 mmol/mol; $P < 0.0001$), respectively. The effect of DKA was also independent of insulin pump use or having a parent or sibling with type 1 diabetes, which predicted lower HbA_{1c} by 0.4% (4.4 mmol/mol; $P < 0.0001$) and 0.2% (2.2 mmol/mol; $P = 0.01$), respectively. Family history of diabetes other than type 1 diabetes in a parent or sibling did not predict a change in long-term HbA_{1c} levels.

The dose-response relationship between severity of DKA and average HbA_{1c} during the follow-up was confirmed. Specifically, there was an increase in HbA_{1c} levels over time of 0.9% (9.8 mmol/mol) for those diagnosed in mild/moderate DKA and a 1.4% (15.3 mmol/mol) increase for those in severe DKA. The long-term mean HbA_{1c} levels adjusted for age, race/ethnicity, sex, insurance status, family history of diabetes, and insulin pump use (Supplementary Fig. 1) were similar to unadjusted patterns (Fig. 2).

CONCLUSIONS

The major novel finding of this study is the sustained negative effect of DKA at diagnosis of type 1 diabetes in children on glycemic control during the following 15 years. Importantly, this effect is independent of demographic and socioeconomic factors (younger age, ethnic minority status, male sex) or access to care barriers that are associated with both DKA and long-term glycemic control. The dose-response effect of DKA severity on future poor glycemic control strengthens the evidence for causality. Therefore, DKA at diagnosis of type 1 diabetes is not just an acute complication but is also a harbinger of increased morbidity and mortality associated with poor glycemic control. Consequently, effective prevention of DKA at diagnosis may provide enduring benefits. Future studies are warranted to assess the effectiveness of DKA prevention at type 1 diabetes onset on improving long-term glycemic control.

Our study confirmed previously known risk factors for DKA at diagnosis of childhood type 1 diabetes (Table 1). Children that presented in DKA were younger than those who presented with milder symptoms, and younger age predicted higher HbA_{1c} over time (0.5% [5.5 mmol/mol] per 10 years in age at diagnosis), similar to previous studies (21,22). Consistent with other studies (1,23), we found a high percentage of children diagnosed in DKA were nonwhite or Hispanic and had government-provided or no medical insurance. These associations are likely



Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
DKA	1297	1155	1097	1063	981	834	712	607	481	384	314	241	173	135	94	67

Figure 1—DKA at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

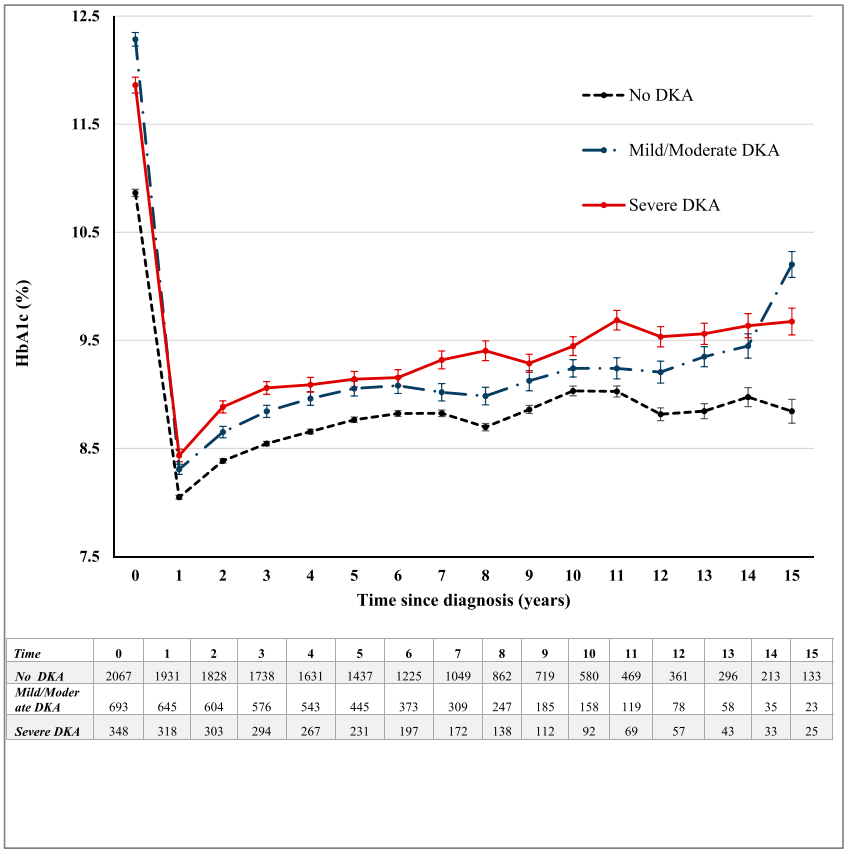
multifactorial and inherently incorporate language barriers, parental education, socioeconomic status, and cultural inequalities. Although adjusting for insurance status and insulin pump treatment may not fully control for disparities in access to care, the BDC provides the same level of diabetes management to all children, regardless of the family's ability to pay. The Center provides, as needed, free diabetes care supplies (Helping Hands by the Children's Diabetes Foundation) as well as free transportation and parking. Since 2002, the BDC Hispanic/Latino Childhood Diabetes Program has provided bilingual culturally sensitive diabetes care service for Spanish-speaking and bilingual families. Therefore, it is unlikely that disparate access to care could explain the observed sustained differences in HbA_{1c} over time.

In support of the observed reduction in HbA_{1c} levels from insulin pump use (continuous subcutaneous insulin infusion) shown in this study, previous studies performed in similarly aged cohorts with comparable follow-up time found a decrease in HbA_{1c} level of 0.6% (6.6 mmol/mol) from 1998 to 2005 (24) and an even larger reduction of 1.5% (16.4 mmol/mol) from 2000 to 2011 (25). The rate of DKA was found to be the lowest among children or siblings of people with type 1 diabetes, which illustrates the importance of parental awareness of signs and symptoms of diabetes. However, having a first-degree relative was not an independent predictor of HbA_{1c} in children diagnosed without DKA in this study ($P = 0.22$) and was found to increase post diagnosis HbA_{1c} in Danish children who have a low prevalence of DKA at diagnosis (11). We have shown predictors of higher HbA_{1c} over time, independent of DKA status at onset, include increased age, female sex, minority race/ethnicity, and being on government insurance or having no insurance compared with private insurance. These results highlight lifestyle factors other than DKA that can be targeted to reduce poor glycemic control over time. In addition, all of these factors have been shown to affect social contributors of poor glycemic control in children and adolescents with type 1 diabetes (26).

Several studies have demonstrated that early glycemic control is of paramount importance to the prevention of diabetic complications (12,13). The Diabetes Control and Complications Trial (DCCT) demonstrated that the mean HbA_{1c} level during the trial was the overriding predictor of retinopathy progression and that even what appeared to be minimal changes in HbA_{1c} levels actually translated into large reductions in the risk of complications (27–29). More specifically, the DCCT study showed that a 10% reduction in HbA_{1c} was associated with a 44% lower risk of retinopathy progression and that this relationship applied over the range of HbA_{1c} values (27). A 1.4% (15.3 mmol/mol) difference in HbA_{1c} levels observed in the current study between the severe DKA group and no DKA group, at the HbA_{1c} of 9.5% (80 mmol/mol), translates to a 13% reduction in HbA_{1c} and an ~50% reduction of retinopathy.

Exacerbated loss of β-cells is the most plausible mediator of the powerful effect of DKA at diagnosis on long-term glycemic control. Severe hyperglycemia and systemic inflammation associated with DKA augments damage from prolonged autoimmune destruction and further depletes functional pancreatic islets (8). This leads to lower residual β-cell function (9) and worse glycemic control despite higher insulin requirements (10). Children who experience DKA can exhibit long-term cognitive complications, which in turn adversely influence their ability to engage in self-care. Ghetti et al. (3) assessed memory deficits in 33 children with type 1 diabetes who suffered at least one episode of DKA and found that children with DKA history had a significantly lower ability to recall events in association with specific details, as tested by event-color and event-spatial position associations. Furthermore, when cognitive problems persist into late adolescence, there is evidence indicating greater risk for poor diabetes management during early adulthood (30,31), which is in turn associated with chronic hyperglycemia (32).

Development of islet autoantibodies occurs before clinical diagnosis of type 1 diabetes, making type 1 diabetes a predictable disease in an individual with two or more autoantibodies (33). Screening



Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No DKA	2067	1931	1828	1738	1631	1437	1225	1049	862	719	580	469	361	296	213	133
Mild/Moderate DKA	693	645	604	576	543	445	373	309	247	185	158	119	78	58	35	23
Severe DKA	348	318	303	294	267	231	197	172	138	112	92	69	57	43	33	25

Figure 2—DKA severity at diagnosis of children with type 1 diabetes and long-term glycemic control. The numbers reported below the figure represent the number of participants contributing the overall HbA_{1c} level during that point in time. Data presented are mean ± SE from unadjusted linear mixed model.

children for the presence of islet autoantibodies and close monitoring of those who are positive can prevent 80–90% of DKA, especially among children with no family history of diabetes (34,35). General population screening for islet autoantibodies, combined with a community awareness campaign, has been shown to be effective and feasible in preventing DKA (36), highlighting that DKA is a modifiable risk factor that can be targeted to improve glycemic control over time in children with type 1 diabetes.

The current study has inherent strengths and limitations. The main strength of this study is that it was performed in a large cohort of children with type 1 diabetes that have been monitored for a long time using standardized methods. In addition, this study is externally valid in that it is generalizable to the entire state of Colorado. However, there are some limitations because we do not have reliable data on insulin analogs or insulin dose over time. It would be of interest to examine changes in insulin dose–adjusted HbA_{1c} over time. To ultimately prove the postulated effect of DKA on residual endogenous insulin secretion, serial C-peptide measurements will be needed in future studies. It is possible there are metabolic or physiologic differences in the rate or severity of the β-cell damage that then lead to the development of DKA and consequently also account for the poorer long-term glycemic control. For example, differences have been observed in complement levels; specifically, higher plasma complement C4A protein concentrations were associated with higher levels of stimulated C-peptide at 1 month post diabetes diagnosis, whereas those with higher C4B levels were less likely to retain the capability to secrete endogenous insulin at 9 months post diagnosis (37). Finally, we have not

Table 2—Predictors of longitudinal HbA_{1c} levels during follow-up for up to 15 years in children with type 1 diabetes*

Predictor of HbA_{1c}	HbA_{1c} % (mmol/mol) estimate	HbA_{1c} % (mmol/mol) 95% CI	*P* value
DKA at diagnosis			
None	Ref.	—	—
Mild/moderate	0.87 (9.5)	0.71–1.03 (7.8–11.3)	<0.0001
Severe	1.35 (14.8)	1.23–1.47 (13.4–16.1)	<0.0001
Age at diagnosis (years)	0.05 (0.5)	0.04–0.06 (0.4–0.7)	<0.0001
Male sex	−0.17 (−1.9)	−0.25 to −0.08 (−2.7 to −0.9)	0.0001
Ethnicity			
Non-Hispanic white	Ref.	—	—
Other	0.48 (5.2)	0.38–0.59 (4.2–6.4)	<0.0001
Insurance status			
Private	Ref.	—	—
Government	0.20 (2.2)	0.03–0.37 (0.3–4.0)	0.02
None	0.22 (2.4)	0.11–0.33 (1.2–3.6)	<0.0001
Insulin pump use (yes)	−0.41 (−4.5)	−0.50 to −0.32 (−5.5 to −3.5)	<0.0001
Family history			
No family history of diabetes	Ref.	—	—
Parent or sibling with type 1 diabetes	−0.19 (−2.1)	−0.34 to −0.05 (−3.7 to −0.5)	0.01
Other family history of diabetes	−0.04 (−0.4)	−0.13 to 0.05 (−1.4 to 0.5)	0.39

*Results show either an increase or decrease in mean HbA_{1c} levels associated with the predictor, from a linear mixed-effects model, with all predictors analyzed simultaneously.

adjusted the analyses for recurrent DKA that occurs more often in patients initially diagnosed with DKA and may further deteriorate residual insulin secretion.

In summary, this study demonstrated that DKA (mild/moderate or severe) in children diagnosed with type 1 diabetes was associated with higher long-term HbA_{1c} levels during follow-up compared with the children who were not in DKA when diagnosed with type 1 diabetes. Lower residual insulin secretion in children presenting with DKA may be at fault and could be prevented with earlier diagnosis.

Acknowledgments. The study was performed at the Barbara Davis Center for Diabetes in Denver, CO, and at the Children's Hospital Colorado.

Funding. Support for the study was provided by the Children's Diabetes Foundation and the Richard S. Abrams Endowment for Clinical Research.

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

Author Contributions. L.M.D. researched data, analyzed data, and wrote the manuscript. B.W. was involved in data management. M.R. and A.R. designed the study, researched data, contributed to the discussion, and reviewed the manuscript. A.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

References

1. 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
2. Rewers A, Dong F, Slover RH, Klingensmith GJ, Rewers M. Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012. JAMA 2015;313:1570–1572
3. Ghetti S, Lee JK, Sims CE, Demaster DM, Glaser NS. Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes. J Pediatr 2010;156:109–114
4. Cameron FJ, Scratch SE, Nadebaum C, et al.; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care 2014;37:1554–1562
5. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011;343:d4092
6. 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
7. Baldelli L, Flitter B, Pyle L, et al. A survey of youth with new onset type 1 diabetes: opportunities to reduce diabetic ketoacidosis. Pediatr Diabetes 11 October 2016 [Epub ahead of print]. https://doi.org/10.1111/pedi.12455
8. Atkinson MA, Bluestone JA, Eisenbarth GS, et al. How does type 1 diabetes develop? The notion of homicide or β-cell suicide revisited. Diabetes 2011;60:1370–1379
9. Fernandez Castañer M, Montaña E, Camps I, et al. Ketoacidosis at diagnosis is predictive of lower residual beta-cell function and poor metabolic control in type 1 diabetes. Diabetes Metab 1996;22:349–355
10. 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
11. Fredheim S, Johannesen J, Johansen A, et al.; Danish Society for Diabetes in Childhood and Adolescence. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia 2013;56:995–1003
12. Rudberg S, Ullman E, Dahlquist G. Relationship between early metabolic control and the development of microalbuminuria—a longitudinal study in children with type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1993;36:1309–1314
13. Svensson M, Eriksson JW, Dahlquist G. Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden. Diabetes Care 2004;27:955–962
14. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994;125:177–188
15. Steffes MW, Sibley S, Jackson M, Thomas W. β-Cell function and the development of diabetes-related complications in the Diabetes Control and Complications Trial. Diabetes Care 2003;26:832–836
16. Wood JR, Miller KM, Maahs DM, et al.; T1D Exchange Clinic Network. Most youth with type 1 diabetes in the T1D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. Diabetes Care 2013;36:2035–2037
17. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
18. Livingstone SJ, Levin D, Looker HC, et al.; Scottish Diabetes Research Network epidemiology group; Scottish Renal Registry. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA 2015;313:37–44
19. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–1982
20. Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatr Diabetes 2009;10(Suppl. 12):118–133
21. Helgeson VS, Siminerio L, Escobar O, Becker D. Predictors of metabolic control among adolescents with diabetes: a 4-year longitudinal study. J Pediatr Psychol 2009;34:254–270
22. Urbach SL, LaFranchi S, Lambert L, Lapidus JA, Daneman D, Becker TM. Predictors of glucose control in children and adolescents with type 1 diabetes mellitus. Pediatr Diabetes 2005;6:69–74
23. 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
24. de Beaufort CE, Swift PG, Skinner CT, et al.; Hvidoere Study Group on Childhood Diabetes 2005. Continuing stability of center differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? The Hvidoere Study Group on Childhood Diabetes. Diabetes Care 2007;30:2245–2250
25. Dovc K, Telic SS, Lusa L, et al. Improved metabolic control in pediatric patients with type 1 diabetes: a nationwide prospective 12-year time trends analysis. Diabetes Technol Ther 2014;16:33–40
26. Delamater AM, de Wit M, McDarby V, Malik J, Acerini CL; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Psychological care of children and adolescents with type 1 diabetes. Pediatr Diabetes 2014;15(Suppl. 20):232–244
27. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes 1995;44:968–983
28. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group; Lachin JM, White NH, Hainsworth DP, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–642
29. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial—revisited. Diabetes 2008;57:995–1001
30. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunger DB. Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. Diabetes Care 2001;24:1536–1540
31. Wysocki T, Hough BS, Ward KM, Green LB. Diabetes mellitus in the transition to adulthood: adjustment, self-care, and health status. J Dev Behav Pediatr 1992;13:194–201
32. Northam EA, Anderson PJ, Werther GA, Warne GL, Andrewes D. Predictors of change in the neuropsychological profiles of children with type 1 diabetes 2 years after disease onset. Diabetes Care 1999;22:1438–1444
33. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
34. 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
35. Elding Larsson H, Vehik K, Bell R, et al.; TEDDY Study Group; SEARCH Study Group; Swediabkids Study Group; DPV Study Group; Finnish Diabetes Registry Study Group. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. Diabetes Care 2011;34:2347–2352
36. Raab J, Haupt F, Scholz M, et al.; Fr1da Study Group. Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study. BMJ Open 2016;6:e011144
37. Kingery SE, Wu YL, Zhou B, Hoffman RP, Yu CY. Gene CNVs and protein levels of complement C4A and C4B as novel biomarkers for partial disease remissions in new-onset type 1 diabetes patients. Pediatr Diabetes 2012;13:408–418