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ORIGINAL ARTICLE

Diabetic Ketoacidosis at Diagnosis in Youth with Type 1 Diabetes Is Associated with a Higher Hemoglobin A1c Even with Intensive Insulin Management

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Abstract

Introduction: Diabetic ketoacidosis (DKA) at diagnosis is associated with short- and long-term complications. We assessed the relationship between DKA status and hemoglobin A1c (A1c) levels in the first year following type 1 diabetes (T1D) diagnosis.

Research Design and Methods: The Pilot Teamwork, Targets, Technology, and Tight Control (4T) study offered continuous glucose monitoring to youth with T1D within 1 month of diagnosis. A1c levels were compared between historical ($n = 271$) and Pilot 4T ($n = 135$) cohorts stratified by DKA status at diagnosis (DKA: historical = 94, 4T = 67 versus without DKA: historical = 177, 4T = 68). A1c was evaluated using locally estimated scatter plot smoothing. Change in A1c from 4 to 12 months postdiagnosis was evaluated using a linear mixed model.

Results: Median age was 9.7 (interquartile range [IQR]: 6.6, 12.7) versus 9.7 (IQR: 6.8, 12.7) years, 49% versus 47% female, 44% versus 39% non-Hispanic White in historical versus Pilot 4T. In historical and 4T cohorts, DKA at diagnosis demonstrated higher A1c at 6 (0.5% [95% confidence interval (CI): 0.21–0.79; $P < 0.01$] and 0.38% [95% CI: 0.02–0.74; $P = 0.04$], respectively), and 12 months (0.62% [95% CI: −0.06 to 1.29; $P = 0.07$] and 0.39% [95% CI: −0.32 to 1.10; $P = 0.29$], respectively). The highest % time in range (TIR; 70–180 mg/dL) was seen between weeks 15–20 (69%) versus 25–30 (75%) postdiagnosis for youth with versus without DKA in Pilot 4T, respectively.

Conclusions: Pilot 4T improved A1c outcomes versus the historical cohort, but those with DKA at diagnosis had persistently elevated A1c throughout the study and intensive diabetes management did not mitigate this difference. DKA prevention at diagnosis may translate into better glycemic outcomes in the first-year postdiagnosis.

Clinical Trial Registration: clinicaltrials.gov: NCT04336969.

Keywords: Type 1 diabetes, Diabetic ketoacidosis, Pediatrics, Continuous glucose monitoring, Hemoglobin A1c.

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Introduction

DIABETIC KETOACIDOSIS (DKA) is a potentially life-threatening complication of type 1 diabetes (T1D) that can occur at diagnosis or later in the course of the condition.[1] Based on clinical guidelines, the diagnosis of DKA is defined as a venous pH <7.3 or serum bicarbonate <15 mmol/L.[2,3] Although DKA rates at diagnosis remain high globally, the relationship with long-term glycated hemoglobin A1c (HbA1c) levels has not been consistently established. Clapin et al.[4] recently demonstrated that severe DKA at T1D diagnosis was associated with a marginally elevated HbA1c over time in a large prospective cohort of children and young adults. Another recent meta-analysis by Alfayez et al.[5] revealed a 35% higher risk of DKA, and specifically, 76% higher risk of severe DKA among pediatric patients with T1D. These findings underscore the need for increased vigilance and preventive measures to address the significant rise in DKA risk.

The Teamwork, Targets, Technology, and Tight Control (4T) study was developed at Stanford to intensify diabetes management during the first year of T1D diagnosis and improve long-term outcomes.[6,7] This program is ongoing and starts newly diagnosed youth with T1D on continuous glucose monitoring (CGM) technology within the first month of diagnosis and additional remote patient monitoring. Our team has previously demonstrated that youth with new-onset T1D in the Pilot 4T program have significantly lower HbA1c at 12 months postdiagnosis when compared to the historical cohort.[6] In addition, we reported that clinically significant hypoglycemia was infrequent over 12 months postdiagnosis.[8]

Our aim with the present analysis was to determine the relationship between DKA status at diagnosis and HbA1c in the first year following T1D in a historical cohort and one that was intensively managed and achieved tighter glucose values. Our goal was to determine whether the effect of DKA at presentation on HbA1c in the first year could be overcome by intensive management.

Research Design and Methods

Study design and participants

The historical cohort ($n = 272$) consisted of youth newly diagnosed with T1D between June 2014 and December 2016 that received standard education and quarterly clinic visits thereafter.[6] One participant in the historical cohort did not have any DKA presentation information available and was therefore excluded from the analysis ($n = 271$). The Pilot 4T cohort ($n = 135$) consisted of all youth with newly diagnosed T1D that were offered CGM within the first month of diagnosis between July 2018 and June 2020.[6] The 4T Program is described in more detail elsewhere[7] and comprised CGM initiation shortly after diabetes diagnosis, psychosocial assessment via patient reported outcomes, and remote monitoring of glucose data with dose changes as clinically indicated.

Based on standard of care guidelines, a clinical diagnosis of DKA was defined as (1) hyperglycemia: blood glucose level >200 mg/dL; (2) ketosis: serum ketone level ≥3 mmol/L or urine ketones ≥2+ (''moderate'' or ''large''), and (3) acidosis: venous pH <7.3 or serum bicarbonate <15 mmol/L.[2,9]

In a subset of historical participants ($n = 3$), although there was no pH or bicarbonate data available at diagnosis within the electronic medical record (EMR), record review by study staff identified narratives in clinical notes denoting their DKA status. A manual of procedures document was created for all 4T research staff to follow and verify DKA status of participants. Clinical DKA for all historical and Pilot 4T cohorts were reviewed by the 4T research staff and confirmation was based on individual chart reviews within the EMR system. An additional and final review was conducted by 4T clinicians and study staff for verification to ensure correct reporting of DKA status. The Stanford University Institutional Review Board approved the study protocol and informed consent were obtained for all participants before study start.

Statistical analysis

A flexible linear mixed-effects regression model that allows for piecewise linear slopes of HbA1c levels to be estimated from diagnosis to 4 months and from 4 to 12 months postdiagnosis was used to assess 4- to 12-month differences by DKA status.[6,10,11] We modeled within-participant correlation through inclusion of a participant-specific random effect, and adjusted for characteristics at diagnosis (age, sex, Hispanic ethnicity, and public insurance). HbA1c trajectories were additionally visualized by DKA status using locally estimated scatter plot smoothing. Statistical hypotheses were two-sided and tested at the 0.05 level of significance. All analyses were conducted in the R statistical computing framework, version 4.2.3.

Exploratory outcomes consisted of CGM metrics, including the glucose percent time in range (70–180 mg/dL), time in hypoglycemia (54–69 mg/dL), and percent time in clinically significant hypoglycemia (<54 mg/dL) from Dexcom Clarity reports. CGM data were systematically collected for youth in the Pilot 4T, but not for the historical cohort, which had a limited and nonsystematic approach to CGM use. As such, CGM metrics were only analyzed for the Pilot 4T cohort. An additional subanalysis included moderate to severe DKA at diagnosis that was defined as serum pH <7.2 or bicarbonate <10 mmol/L[9] in both historical and Pilot 4T cohorts. In the historical cohort, three records were missing both pH and bicarbonate data at diagnosis and were excluded from this exploratory analysis.

Results

The historical cohort ($n = 271$) of youth with T1D was compared with the Pilot 4T cohort ($n = 135$). Participants in the historical cohort ($n = 271$) had a median age of 9.7 (interquartile range [IQR]: 6.6, 12.7) years, 49% female, 44% non-Hispanic White, 73% of private insurance, and 90% English-speaking. Similarly, participants in the Pilot 4T study ($n = 135$) had a median age of 9.7 (IQR: 6.8, 12.7) years, 47% female, 39% non-Hispanic White, 77% on private insurance, and 87% English-speaking (Table 1). CGM was initiated sooner following diagnosis in the Pilot 4T cohort compared to the historical cohort (7 [IQR: 5, 11] days vs. 100 [IQR: 50–172] days, respectively).

In the historical cohort, 94 youth presented in DKA (HbA1c 11.8% ± 2.2%, pH 7.2 [7.0, 7.2], bicarbonate 8.8 [IQR: 5.0, 11.8] mmol/L), and 177 presented without DKA (HbA1c 10.5% ± 2.5%) at diagnosis. In the Pilot 4T cohort, 67 youth presented in DKA (HbA1c 12.6% ± 1.9%, pH 7.1

Table 1. Demographics of Historical and Pilot Teamwork, Targets, Technology, and Tight Control Cohorts

Characteristic	*4T pilot DKA status*			*Historical DKA status*		
	Overall, n = *135*	*Yes,* n = *67*	*No,* n = *68*	*Overall,* n = *271*[a]	*Yes,* n = *94*	*No,* n = *177*
Age at T1D diagnosis, median (Q1–Q3), years	9.7 (6.8–12.7)	9.7 (7.1–12.4)	9.4 (6.6–13.3)	9.7 (6.6–12.7)	9.5 (6.3–12.3)	9.8 (6.7–13.0)
Age group at diagnosis, *n* (%), years						
0.5–6	31 (23.0)	15 (22.4)	16 (23.5)	59 (21.8)	22 (23.4)	37 (20.9)
>6–13	71 (52.6)	37 (55.2)	34 (50.0)	154 (56.8)	58 (61.7)	96 (54.2)
>13–19.9	33 (24.4)	15 (22.4)	18 (26.5)	58 (21.4)	14 (14.9)	44 (24.9)
Sex, *n* (%)						
Female	64 (47.4)	33 (49.3)	31 (45.6)	134 (49.4)	46 (48.9)	88 (49.7)
Male	71 (52.6)	34 (50.7)	37 (54.4)	137 (50.6)	48 (51.1)	89 (50.3)
Race/Ethnicity, *n* (%)						
Non-Hispanic White	53 (39.3)	28 (41.8)	25 (36.8)	120 (44.3)	44 (46.8)	76 (42.9)
Non-Hispanic Black				5 (1.8)	1 (1.1)	4 (2.3)
Hispanic	29 (21.5)	14 (20.9)	15 (22.1)	69 (25.5)	26 (27.7)	43 (24.3)
Asian or Pacific Islander	19 (14.1)	11 (16.4)	8 (11.8)	24 (8.9)	11 (11.7)	13 (7.3)
American Indian or Alaska Native				1 (0.4)	0 (0.0)	1 (0.6)
Other	19 (14.1)	9 (13.4)	10 (14.7)	21 (7.7)	5 (5.3)	16 (9.0)
Unknown/declined to state	15 (11.1)	5 (7.5)	10 (14.7)	31 (11.4)	7 (7.4)	24 (13.6)
Lowest pH, median (Q1–Q3)	7.1 (7.0–7.2)	7.1 (7.0–7.2)	N/A	7.2 (7.0–7.2)	7.2 (7.0–7.2)	N/A
Lowest bicarbonate, median (Q1–Q3)	9.6 (5.0–13.2)	9.6 (5.0–13.2)	N/A	8.8 (5.0–11.8)	8.8 (5.0–11.8)	N/A
BMI-for-age z-score, mean (SD)	0.1 (1.3)	−0.2 (1.4)	0.3 (1.2)	N/A	N/A	N/A
HbA1c (%) at T1D diagnosis, mean (SD)	12.3 (2.1)	12.6 (1.9)	11.9 (2.2)	10.9 (2.5)	11.8 (2.2)	10.5 (2.5)
Insurance type, *n* (%)						
Private	104 (77.0)	51 (76.1)	53 (77.9)	196 (72.9)	65 (69.9)	131 (74.4)
Public	31 (23.0)	16 (23.9)	15 (22.1)	73 (27.1)	28 (30.1)	45 (25.6)
Primary language, *n* (%)						
English	117 (86.7)	55 (82.1)	62 (91.2)	244 (90.0)	82 (87.2)	162 (91.5)
Non-English	18 (13.3)	12 (17.9)	6 (8.8)	27 (10.0)	12 (12.8)	15 (8.5)
CGM initiation within 1 year, *n* (%)	132 (97.8)	64 (95.5)	68 (100.0)	102 (37.6)	32 (34.0)	70 (39.5)
Initiated CGM ≤30 days, *n* (%)	124 (91.9)	60 (89.6)	64 (94.1)	6 (2.2)	1 (1.1)	5 (2.8)
Days to CGM initiation, median (Q1–Q3)	7 (5–11)	8 (6–11)	7 (5–12)	100 (50–172)	100 (51–150)	99 (48–188)
Insulin pump use within 1 year, *n* (%)	48 (35.6)	24 (35.8)	24 (35.3)	89 (32.8)	34 (36.2)	55 (31.1)
Open loop	30 (22.2)	15 (22.4)	15 (22.1)	66 (24.4)	24 (25.5)	42 (23.7)
Predictive low glucose suspend	2 (1.5)	1 (1.5)	1 (1.5)	2 (0.7)	2 (2.1)	0 (0)
Advanced hybrid closed loop	17 (12.6)	8 (11.9)	9 (13.2)	18 (6.6)	8 (8.5)	10 (5.6)
Days to pump initiation, median (Q1–Q3)	142 (91–256)	195 (95–286)	126 (90–181)	178 (111–250)	187 (105–260)	167 (113–242)

[a]Participant (*n* = 1) without DKA was excluded from analysis (*n* = 271).

4T, Teamwork, Targets, Technology, and Tight Control; BMI, body mass index; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; SD, standard deviation; T1D, type 1 diabetes.

[IQR: 7.0, 7.2], bicarbonate 9.6 [IQR: 5.0, 13.2] mmol/L), and 68 presented without DKA (HbA1c 11.9% ± 2.2%) at diagnosis.

Youth in the historical and Pilot 4T cohorts with DKA at diagnosis had a higher starting HbA1c (11.8% ± 2.2%; 12.6% ± 1.9%) compared to youth without DKA (10.5% ± 2.5%; 11.9% ± 2.2%), respectively (Table 1). Youth in the historical cohort achieved comparable nadir HbA1c (7.0% for youth without DKA and 7.1% for youth with DKA) between months 4 and 5 postdiagnosis, whereas Pilot 4T youth achieved nadir HbA1c (6.5% for youth without DKA and 6.9% for youth with DKA) comparatively later, at 6 months (Fig. 1).

Based on the regression analysis, DKA at diagnosis was associated with a 0.50% (95% confidence interval [CI]: 0.21–0.79; $P < 0.01$) higher HbA1c at 6 months and a 0.62% (95% CI: −0.06 to 1.29; $P = 0.07$) higher HbA1c at 12 months in the historical cohort (Fig. 2a). In the Pilot 4T cohort, DKA at diagnosis was associated with a 0.38% (95% CI: 0.02–0.74; $P = 0.04$) higher HbA1c at 6 months and a 0.39% (95% CI: −0.32 to 1.10; $P = 0.29$) higher HbA1c at 12 months (Fig. 2b).

In the Pilot 4T cohort, youth that did not present in DKA at diagnosis showed the highest glucose time in range (between 70 and 180 mg/dL) of 75% in weeks 25–30 postdiagnosis and a slow decrease throughout the study period (Fig. 3). Youth with DKA at diagnosis demonstrated the highest glucose time in range of 69% in weeks 15–20, with a dramatic decrease in glucose time in range by 12 months postdiagnosis. The percent time below range (<54–69 mg/dL and <54 mg/dL) by DKA status for historical and Pilot 4T cohorts remained low throughout the study period, with locally smoothed means below 2.3% for hypoglycemia and below 0.6% for clinically severe hypoglycemia.

We conducted a subanalysis for historical and Pilot 4T cohorts with the inclusion of only those participants that presented in moderate to severe DKA at diagnosis (Supplementary Fig. S1). Based on the regression analysis of adjusted 4–12 months differences, in the Pilot 4T cohort, moderate to severe DKA at diagnosis was associated with a 0.36% (95% CI: −0.05 to 0.78; $P = 0.09$) higher HbA1c at 6 months and a 0.28% (95% CI: −0.48 to 1.04; $P = 0.47$) higher HbA1c at 12 months. Overall differences in HbA1c between the DKA and non-DKA groups were similar after excluding mild cases.

Discussion

In the Pilot 4T study, youth who presented in DKA at diagnosis exhibited higher HbA1c levels compared to those without DKA in the first year of diagnosis. More specifically, DKA at diagnosis was associated with a clinically meaningful higher HbA1c at 6 and 12 months of nearly 0.4%. Although we noted a higher incidence of DKA in the Pilot 4T cohort compared to the historical cohort, the underlying etiology remains unknown. Even with the implementation of an intensive diabetes management program, the difference in elevation in HbA1c levels between the DKA and non-DKA groups was not eliminated. As such, DKA presentation at diagnosis may serve as a marker for physiological (i.e., reduced C-peptide levels or beta-cell insult), psychosocial, and

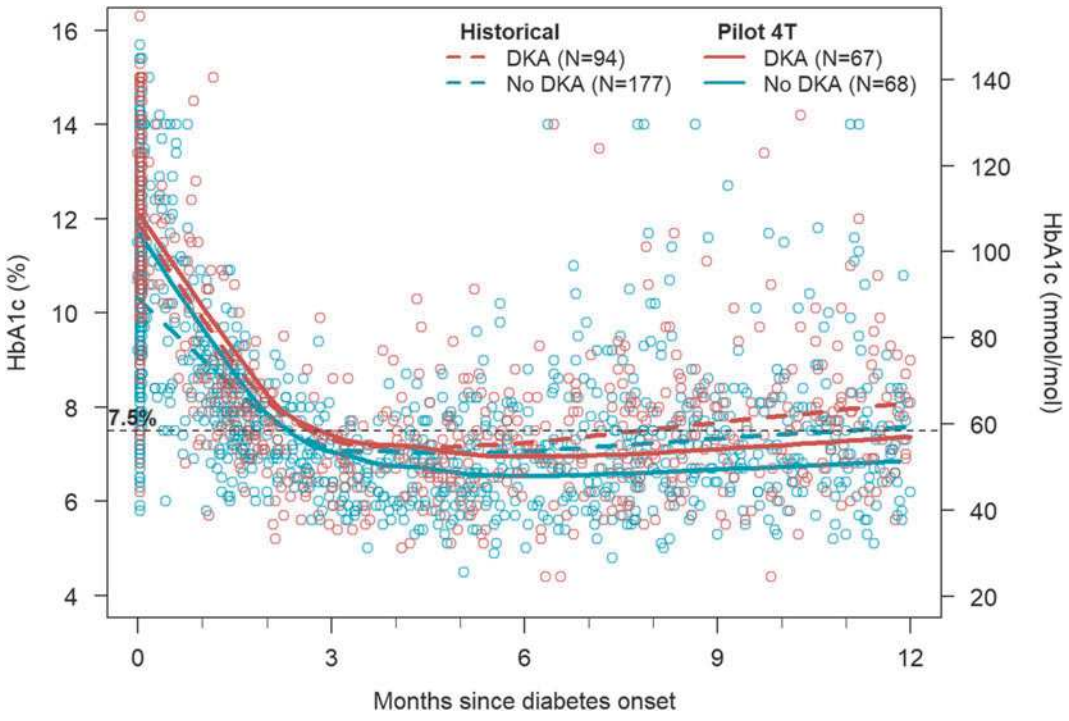

FIG. 1. Scatter plot of HbA1c values (%) for youth in the historical and Pilot 4T cohorts across the first 12 months of T1D diagnosis by DKA status, with LOESS. The red lines represent those youth with DKA present at diagnosis, and the blue lines represent no DKA at diagnosis. The solid lines represent the Pilot 4T cohort and dashed lines represent the historical cohort. 4T, Teamwork, Targets, Technology, and Tight Control; DKA, diabetic ketoacidosis; HbA1c, hemoglobin A1c; LOESS, locally estimated scatter plot smoothing; T1D, type 1 diabetes.

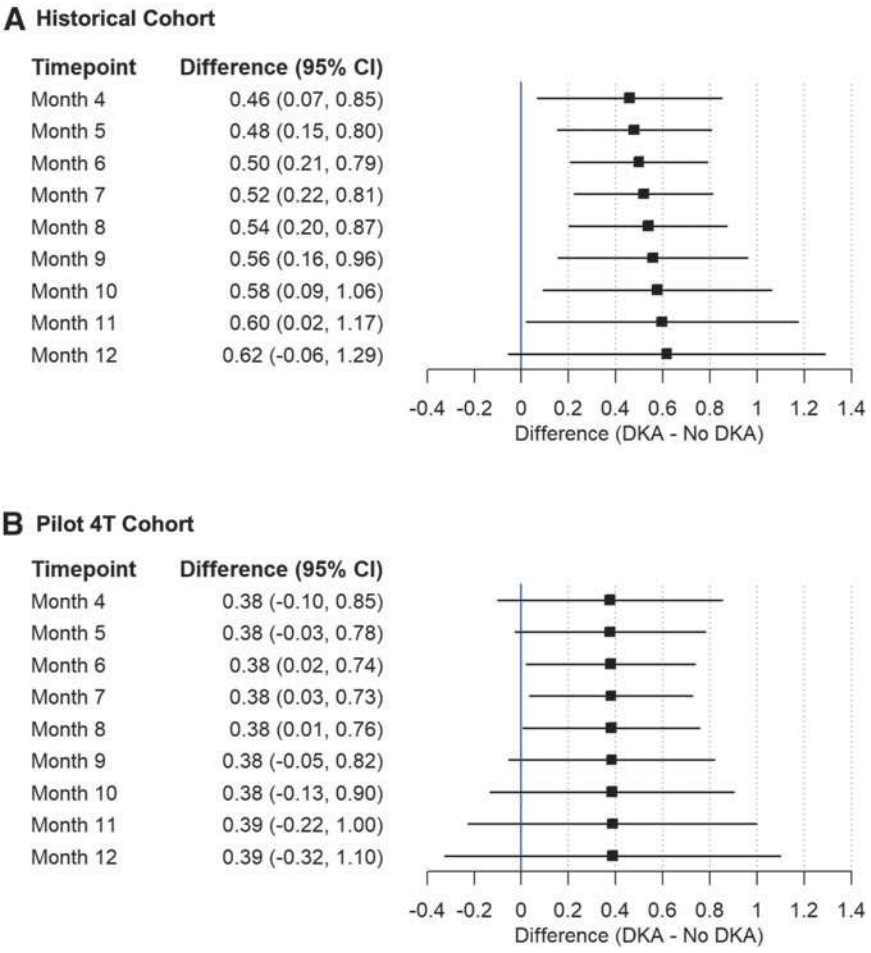

FIG. 2. Monthly differences (DKA minus no DKA) in HbA1c from baseline covariate-adjusted linear mixed-effects regression model for youths in the historical **(A)** versus Pilot 4T **(B)** cohort.

family-related factors that contributes to challenges in achieving lower HbA1c levels.

The 4T study implemented a multidisciplinary, team-based approach to start newly diagnosed youth with T1D on CGM within the first month following a diabetes diagnosis, supplemented by a weekly population health dashboard for remote patient monitoring. This comprehensive program aimed to significantly improve glycemic outcomes in this population. After 12 months from the initial diabetes diagnosis, our earlier work has revealed marked improvements in glycemic outcomes among youth in this study.[6] However, despite the implementation of this unique, intensive diabetes management program, a difference in HbA1c levels between youth with and without DKA at diagnosis remained.

Duca et al.[12] investigated the impact of DKA at diagnosis on long-term glycemic control in children. This study revealed that youth with T1D and DKA (mild/moderate or severe) at diagnosis had persistently higher HbA1c levels over a 15-year follow-up period, independent of demographic and socioeconomic factors. Clapin et al.[9] also investigated the prevalence of moderate to severe DKA at T1D diagnosis and subsequent long-term HbA1c and glycemic outcomes in Western Australia between 2000 and 2019. In contrast, Clapin et al.[4,9] did not find a consistent and clinically significant relationship between DKA at diagnosis and long-term HbA1c levels in Western Australia. These articles highlight the complexity of factors influencing glycemic outcomes in T1D and the need for further research to understand these relationships.

The Diabetes Control and Complications Trial demonstrated that adults with residual beta cell function (measured by C-peptide secretion) generally experience better glycemic outcomes, with a reduced risk of hypoglycemia, and fewer microvascular complications.[13] However, it was unclear whether long-term intensive glucose management following diabetes diagnosis can help to preserve C-peptide secretion in youth with T1D. Greenbaum et al.[14] conducted a study of C-peptide levels during the first 2 years following diagnosis, revealing distinct phases in C-peptide decline. Notably, their study did not find evidence that DKA at diagnosis resulted in lower C-peptide levels during follow-up. Similarly, DiMeglio et al.[15] explored changes in beta cell function within the first 6 weeks postdiagnosis and results also suggested that DKA has not been reported to result in lower C-peptide levels, and therefore, beta-cell function during follow-up.

Boughton et al.[16] recently demonstrated that intensive glucose management for 24 months with the use of a hybrid closed-loop system following T1D diagnosis in youth did not appear to prevent the decline in residual C-peptide secretion. Another recent study by Forlenza et al.[17] demonstrated that verapamil partially preserved stimulated C-peptide secretion at 52 weeks postdiagnosis versus placebo, but this was not accompanied by significant group differences in HbA1c levels at 1 year. However, additional research is necessary to

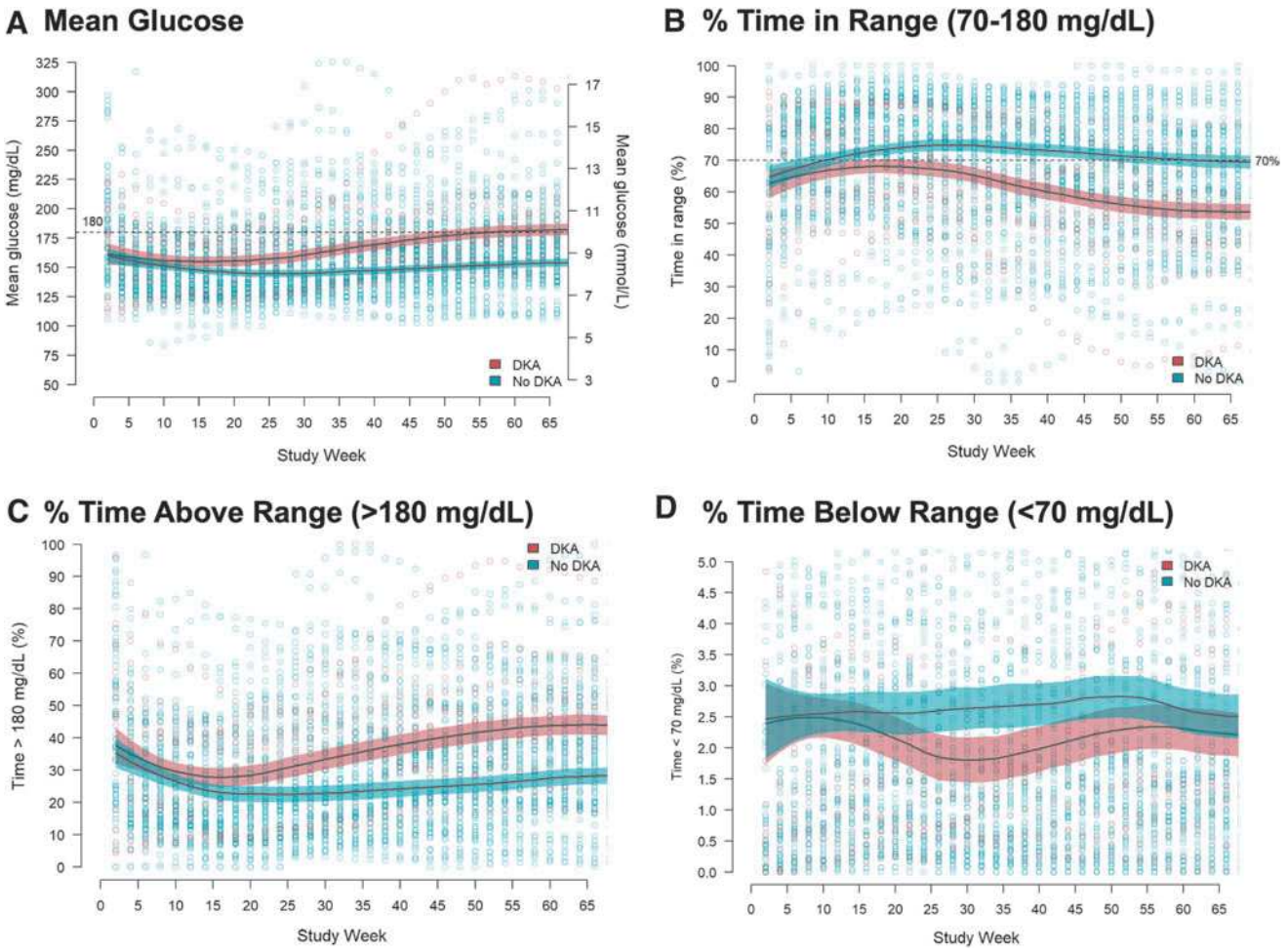

FIG. 3. Scatter plot with pointwise 95% CIs of the **(A)** CGM mean glucose (mg/dL and mmol/L), **(B)** CGM glucose percent time in range (70–180 mg/dL), **(C)** CGM glucose percent time above range (>180 mg/dL), and **(D)** CGM glucose percent time below range (<70 mg/dL) at 2-week intervals in the Pilot 4T cohort stratified by DKA status. CGM, continuous glucose monitoring; CI, confidence interval.

determine whether long-term improvements in C-peptide levels exist and to identify the most effective duration of verapamil therapy. These collective findings underscore the need to better understand the etiology of sustained elevations in HbA1c for individuals who present in DKA at diagnosis. A comprehensive and multifaceted approach to T1D management, encompassing early diagnosis, targeted interventions to prevent DKA, and ongoing efforts to optimize glycemic control are critical.

A greater emphasis is also needed on preventing DKA at diagnosis that could potentially lead to improved glycemic outcomes following T1D diagnosis. One evidence-based method to reduce DKA at presentation is to screen for T1D, either in targeted populations, which has extensive supportive data,[18–20] and in the general population, for which evidence is emerging.[21–23] One of the proven benefits of autoantibody screening to detect preclinical T1D is the reduction in DKA at stage 3 (insulin-requiring) T1D.[24] Another proposed benefit of screening for T1D is to improve long-term outcomes for which tight glycemic control is necessary. Another recent publication from the TrialNet Pathway to Prevention study demonstrated that CGM data also have the potential to optimize the identification of first-degree family members who are at a higher risk of developing T1D.[25]

This project has several key strengths and limitations worth noting. A strength of this study includes our multidisciplinary team approach, including, but not limited to, clinicians, clinical psychologists, Certified Diabetes Care and Education Specialists, engineers, and an exercise physiologist. In addition, the 4T study proactively reached out to all eligible youth diagnosed with new-onset T1D within our clinic, eliminating specific exclusion criteria to ensure an equitable and inclusive study design. Another important strength is that both our historical and Pilot 4T cohorts are generally more diverse (<50% non-Hispanic White) than other technology-based studies in pediatric T1D populations. The 4T study also secured philanthropic funding to cover the first year of CGM expenses, reducing financial barriers, particularly for youth without compatible smartphone devices or CGM coverage.

The limitation includes the current single-center design of this study, although efforts for scaling the 4T program more broadly to additional centers are underway. In addition, CGM technology has advanced during the time periods assessed

(historical to Pilot 4T) and therefore, it is important that our future work also compares outcomes with more recent cohorts using similar CGM devices. Another limitation with the present work is that the relationship between DKA status at diagnosis and HbA1c in the first year following T1D diagnosis was not our primary study focus. It is also possible that youth with DKA at diagnosis may have had less beta cell function persisting throughout the first year following diagnosis, resulting in worse glycemic outcomes. However, we did not systematically measure C-peptide levels in new onset youth at T1D diagnosis and, therefore, are unable to draw definitive conclusions on the differences between these cohorts.

Importantly, in the Pilot 4T study, our primary endpoints were HbA1c and CGM metrics, not specifically on beta-cell preservation, so collecting C-peptide at or near diagnosis was not part of the original study design. As such, this is an opportunity for the ongoing 4T program to streamline and emphasize the importance of additional support and care needed for youth that present in DKA at diagnosis.

Conclusions

We demonstrate that DKA at diagnosis was associated with higher HbA1c at 6 and 12 months in both historical and Pilot 4T cohorts, reiterating the concern that DKA at diagnosis leads to sustained adverse glycemic outcomes. Despite the implementation of an intensive diabetes management program, the disparity in HbA1c levels between youth with and without DKA at diagnosis persisted. These data highlight the need for additional efforts to prevent DKA at diagnosis and to support youth who present in DKA at diagnosis. In summary, programs to diagnose T1D before the development of DKA, including expansion of T1D screening programs, and clinical and research programs to help youth achieve recommended clinical HbA1c targets can be a potential solution to improve glycemic outcomes.

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Authors' Contributions

D.P.Z. and D.M.M. contributed to the concept of the study. V.Y.D. performed the statistical analyses. D.P.Z. wrote the initial article with critical contributions from coauthors. All authors contributed to article revisions and approved the final submitted article.

Author Disclosure Statement

D.P.Z. has received honoraria for speaking engagements from Ascensia Diabetes, Insulet Canada, and Medtronic Diabetes. D.P.Z also serves as a member of the Dexcom Advisory Board. D.M.M. has had research support from the National Institutes of Health (NIH) and NSF and his institution has had research support from Dexcom, Inc. D.M.M. has consulted for Abbott, the Helmsley Charitable Trust, Lifescan, Sanofi, Medtronic, Provention Bio, Kriya, and Bayer. K.K.H. reported receiving personal fees from Cecelia Health and Dexcom, Inc., and consulting fees from the Lilly Innovation Center, LifeScan Diabetes Institute, and MedIQ outside the submitted work. M.D. has reported receiving grants from the NIH during the conduct of the study.

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Supplementary Material

Supplementary Figure S1

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