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Dysglycemia among youth with type 1 diabetes and suboptimal glycemic control in The Flexible Lifestyle Empowering Change (FLEX) trial

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Abstract

Objective—To examine the prevalence and correlates of non-severe hypoglycemia in adolescents with type 1 diabetes and suboptimal glycemic control, an understudied topic in this group.

Methods—Seven days of blinded continuous glucose monitor data were analyzed in 233 adolescents at baseline of the Flexible Lifestyle Empowering Change (FLEX) trial (13–16 years, type 1 diabetes duration >1 year, and hemoglobin A1c (HbA1c) 8–13% [64–119 mmol]). Incidence of clinical hypoglycemia (54–69 mg/dL) and clinically serious hypoglycemia (<54 mg/dL) was defined as number of episodes ≥15 min. Logistic regression modeling determined correlates of long duration of hypoglycemia, categorized by median split among those who experienced hypoglycemia.

Results—The sample was 76.1% non-Hispanic white, 49.8% female, age=14.9±1.1 years, diabetes duration=6.4±3.7 years and HbA1c=9.6±1.2% [81±13 mmol/mol]. Over 7-days, 79.4% of youth experienced ≥1 hypoglycemic episodes of <70 mg/dL and 55.4% of youth experienced ≥1 hypoglycemic episodes of <54 mg/dL. Among all adolescents, the median duration of clinical hypoglycemia and clinically serious hypoglycemia was 21.9 (range 0–250.2) and 4.3 (range 0–209.7) min/day, respectively. Long duration of clinical hypoglycemia (range 1.8–17.4% time overall) and clinically serious hypoglycemia (range 1.2–14.6% time overall) was associated with

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older age and decreasing HbA1c. Long duration of clinically serious hypoglycemia also was associated with insulin pump use.

Conclusions—Almost 80% of adolescents with elevated HbA1c had an episode of clinical hypoglycemia and >50% had clinically serious hypoglycemia in a week. Increased education alongside access to emerging diabetes technologies may help to prevent hypoglycemia while improving glycemic control.

Keywords

Diabetes Mellitus, Type 1; Hypoglycemia; Blood Glucose; Glycated Hemoglobin A

The primary goals of treatment for individuals with type 1 diabetes is to maximize time of glucose values in target range, achieve an HbA1c as low as possible, minimize hypoglycemia, and optimize quality of life (1). However, hypoglycemia is a major barrier to obtaining optimal glycemic control (2, 3). The DCCT trial provided landmark evidence that severe hypoglycemia increased in a curvilinear manner with lower hemoglobin A1c (HbA1c) (4, 5). However, current data from multiple large pediatric registries have demonstrated a flattening of this curve in the relationship of severe hypoglycemia to HbA1c (6–8).

Recently, the International Hypoglycemia Study Group (IHSG) standardized definitions of hypoglycemia (6, 9, 10). Prior to the use of continuous glucose monitors (CGM) that provide glucose values every 5–15 minutes, episodes of non-severe hypoglycemia (<70 mg/dL, but not associated with severe cognitive impairment requiring external assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions) were not thoroughly captured in outpatient settings (9). To date, the majority of CGM data on hypoglycemia in adolescents with type 1 diabetes have come from diabetes technology clinical trials where study criteria excluded participants with elevated HbA1c levels (typically 9.0 or 10.0%) resulting in study samples with mean HbA1c levels <9.0%, and typically ranging from 7.0 to 8.6% (11). However, mean HbA1c levels in the Type 1 Diabetes Exchange (which includes all HbA1c levels) peak in adolescence and exceed 9.0% (12). Therefore, the CGM data from completed diabetes technology clinical trials may not be broadly generalizable to all adolescents with type 1 diabetes, as the majority of the individuals in this age range do not meet clinical targets for glycemic control and often have HbA1c levels >9% (13).

Although an elevated HbA1c is common in adolescents with type 1 diabetes, data on the frequency of non-severe hypoglycemia in this population is limited (14). Understanding patterns of dysglycemia that are associated with suboptimal HbA1c may inform more specific strategies to improve overall glycemic control, including the prevention of hypoglycemia (2, 15). Therefore, the objective of this study was to examine the incidence, duration, and correlates of non-severe hypoglycemia in a sample of adolescents with type 1 diabetes (HbA1c range 8.0–13.0%, as per inclusion criteria) who wore CGM in a one-week period at baseline from the Flexible Lifestyle Empowering Change (FL3X) randomized clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01286350) identifier: NCT01286350).

Research Design and Methods

Study Sample

Data were analyzed from the baseline visit of the Flexible Lifestyles Empowering Change randomized trial (FLEX). FLEX was a randomized clinical trial testing an adaptive intervention which included behavioral and problem-solving skills for youth with type 1 diabetes over 18 months, with respect to HbA1c (primary outcome), cardiovascular disease risk factors, health-related quality of life, and cost effectiveness. The study design of FLEX has been described elsewhere (16)(17). Eligible participants were youth ages 13–16 years with type 1 diabetes for ≥1 year, literacy in English, HbA1c 8.0–13.0% [64–119 mmol/mol], with no other serious medical conditions or pregnancy and ≥1 primary caregiver willing to participate (16). Participants were recruited from 05/01/2014 to 04/04/2016 at two sites: the Barbara Davis Center for Childhood Diabetes in Colorado and Cincinnati Children's Hospital Medical Center in Ohio, coordinated by the University of North Carolina (UNC) at Chapel Hill (16)(17). Eligibility criteria were based off of most recent point-of-care HbA1c measures in the medical record, where youth with type 1 diabetes were eligible and targeted for recruitment if they had an HbA1c measure of 8.0–13.0% [64–119 mmol/mol]. These youth were targeted for a two-step recruitment process and enrolled in the trial, after which time they had the baseline visit. Participants were not excluded based on the HbA1c value measured at the baseline visit. Therefore, baseline HbA1c measures may exceed the 8.0–13.0% [64–119 mmol/mol] range for eligibility.

Inclusion Criteria

FLEX enrolled 258 adolescents with type 1 diabetes who were instructed to wear a blinded CGM for 7 days at baseline. Participants were excluded from the present analyses if they reported a severe hypoglycemic event (defined as an episode of hypoglycemia requiring external aid) during the study week (n=0) or if there was not CGM data available at the baseline visit, for example if youth did not complete the minimum wear-time of 24 hours or did not return the CGM (n=23). One participant was excluded as an outlier for duration of clinically serious hypoglycemia (percent of time spent <54 mg/dL) for >20% of 7-day wear time. Excluded participants were not significantly different with regards to age, sex, race/ethnicity, health insurance status, parental education, diabetes duration, baseline HbA1c, nor any psychosocial measures but had lower mean measures of BMIz (p=0.002).

Measures

Laboratory data—A central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA, USA) provided oversight and conducted all assays. At all timepoints, HbA1c was measured in whole blood using an automated nonporous ion exchange HPLC system (model G-7; Tosoh Bioscience).

Clinical Measures—Height was measured using a stadiometer, and weight was measured to the nearest 0.1 kg using an electronic scale. Body mass index (BMI, weight (kg) / height (m)²) was calculated and then converted to an age- and sex-specific BMI z-score according to the Centers for Disease Control and Prevention growth charts.

Questionnaires—Standardized questionnaires were used to collect self-reported data including race/ethnicity, highest level of parental education, duration of type 1 diabetes, insulin delivery method (pump versus MDI), and previous CGM use. Self-reported race and ethnicity was classified as non-Hispanic white, non-Hispanic Black, Black, and other including Asian/Pacific Islander, Native American, or unknown. History of severe hypoglycemia in the past 6 months (defined as any episode requiring help of another person) was self-reported and classified as yes or no. Diabetes adherence during the previous three months was measured by the Diabetes Self-Management Profile – Self Report (DSMP-SR) across five domains: exercise, management of hypoglycemia, diet, blood glucose checking, and insulin administration and dose adjustment; with higher scores indicating more self-management behaviors (18). The DSMP-SR was modified for FLEX participants with updated language and to allow for a single questionnaire to be administered regardless of insulin regimen. Fear of hypoglycemia was assessed by the Hypoglycemia Fear Survey (HFS) and measured in three domains: behaviors used to keep blood glucose high to prevent hypoglycemia (Maintain High BG), worry about helplessness (Worry/Helplessness), and worry about social consequences associated with hypoglycemia (Worry/Social Consequences) (19); higher scores indicate higher levels of fear.

Continuous Glucose Monitoring Measures—A blinded CGM [iPro[®]2 Professional CGM; Medtronic Diabetes, Northridge, CA; median absolute relative difference: 11.1% (20)] was worn for a 7-day period to measure interstitial glucose levels in real time throughout the day and night. At the baseline visit, study participants inserted the iPro[®]2 CGM system with the Enlite[™] sensor into abdominal subcutaneous adipose tissue. Participants were carefully instructed on the use and maintenance of the CGM and advised to calibrate the sensor before eating and before bed with an iPro2 compatible glucometer (OneTouch[®] Ultra[®] 2). The Enlite[™] sensor measured interstitial glucose level every 5 minutes within the 40–400 mg/dL range. On the last day of the CGM wear week, participants were reminded to send the devices back, using the pre-paid box/envelope provided to them. CGM data were downloaded with CareLink iPro[®] System and uploaded to the coordinating center for data processing. As part of blinding, no communication from the device was available to participants. Cut-points for glucose used to describe hypoglycemia were established according to recommended IHSG values (10, 21). All CGM-variables were stratified by day (6:00 AM – 11:59 PM) and night (12:00 AM – 5:59 AM) (21).

Outcomes

Both the incidence and duration of hypoglycemia were considered to comprehensively capture the experience of hypoglycemia by the frequency of episodes and the overall extent to which it occurred (21). Incidence of clinical hypoglycemia was categorized as the number of episodes when blood glucose was 54–69 mg/dL for 15 minutes throughout the 7-day period of blinded CGM wear time. Incidence of clinically serious hypoglycemia was categorized as the number of episodes when blood glucose was <54 mg/dL for 15 minutes throughout the 7-day period of blinded CGM wear time. Incidence of clinical hypoglycemia (54–69 mg/dL) and clinically serious hypoglycemia (<54 mg/dL) was defined as number of episodes 15 min. Duration of clinical hypoglycemia was defined as proportion of time 69–

54 mg/dL (21) and duration of clinically serious hypoglycemia was defined as percent of time <54 mg/dL over the 7-day period of blinded CGM wear time(21). Duration of hypoglycemia was reported for all youth, regardless of whether they experienced a 15-minute episode of hypoglycemia, as defined previously. These measures are consistent with recent position statements on hypoglycemia by the International Society of Pediatric and Adolescent Diabetes Hypoglycemia Guidelines Writing Group (6, 9, 10).

Statistical Analysis

Data are presented as mean (SD), n (%), or median (25th percentile (Q1), 75th percentile (Q3, range) for variables that were not normally distributed, such as measures of hypoglycemia. Participant characteristics of individuals with no hypoglycemia or short duration of hypoglycemia versus individuals with long duration of hypoglycemia were compared using chi-square and t-tests (Fischer's Exact and Wilcoxon-Mann-Whitney where appropriate). Measures of hypoglycemia were compared between day and night hours using paired t-tests.

Because the hypoglycemia duration variables were right-skewed, a categorical variable was created based on duration of hypoglycemia for both clinical and clinically serious hypoglycemia: none, short duration of hypoglycemia, and long duration of hypoglycemia. Adolescents who experienced no duration of hypoglycemia were classified as none. Short and long duration were calculated based on a median split of duration among those who experienced hypoglycemia. Logistic regression modeling was used to determine correlates of long duration of clinical and clinically severe hypoglycemia. For this analysis, none and short duration of hypoglycemia were combined as the reference group to identify the factors specifically associated with the longest duration of hypoglycemia. Separate models were used for the outcomes of clinical and clinically serious hypoglycemia. Three sequential models were constructed as follows: Model 1 (demographics) included age, sex, and race/ethnicity (non-Hispanic white versus all others), Model 2 (clinical factors) included diabetes duration, insulin regimen (pump versus MDI), BMIz, and HbA1c, and Model 3 (cognitive and behavioral factors) included type 1 diabetes adherence and fear of hypoglycemia subscales (e.g., Maintain High BG, Worry/Helplessness). The Worry/Social Consequences subscale was dropped because of collinearity issues. A p-value of < 0.05 was considered statistically significant. Analyses were conducted using SAS, version 9.4

Results

The final study sample included 233 adolescents with type 1 diabetes. Table 1 presents the characteristics of the study sample. Participants were 76.1% non-Hispanic white and 49.8% female with mean age 14.9±1.1 years and mean type 1 diabetes duration was 6.4±3.7 yrs. Mean HbA1c was 9.6±1.2% [81±13 mmol/mol] and 66% of the sample had an HbA1c >9.0% [75 mmol/mol].

Table 2 presents the hypoglycemia outcomes. During 7-days, 79.4% of youth experienced 1 hypoglycemic episodes <70 mg/dL lasting 15 minutes and 55.4% of youth experienced 1 hypoglycemic episodes <54 mg/dL lasting 15 minutes. Among all adolescents, median duration of clinical hypoglycemia was 21.9 min/day (range 0–250 minutes), while the

median duration of clinically serious hypoglycemia was 4.3 min/day (range 0–210 minutes). The number of episodes of hypoglycemia was more frequent during the day than the night, with small differences in the overall percentage of time spent in hypoglycemic ranges (all $p < 0.001$).

Table 2 also depicts other CGM-derived parameters measured in FLEX participants. The median CGM glucose was 213.7 ± 44.4 mg/dL. On average, participants spent $34.7 \pm 13.6\%$ of time in range (70–180 mg/dL) and $61.5 \pm 15.8\%$ of time above 180 mg/dL. The mean coefficient of variation was $40.0 \pm 7.7\%$. Duration of hyperglycemia and measures of glycemic variability including standard deviation were lower overnight compared to the day (all $p < 0.001$). Duration of hypoglycemia was correlated with the coefficient of variation ($r = 0.78$ for clinical hypoglycemia and $r = 0.63$ for clinically serious hypoglycemia; $p < 0.001$). Sensitivity analyses explored differences in duration of hypoglycemia by sex and race/ethnicity, but there were no significant differences.

A categorical variable was created based on the duration of hypoglycemia. Ninety youth (39.5%) experienced no clinically serious hypoglycemia (0% of time spent < 54 mg/dL), 71 youth (30.5%) experienced a short duration of clinically serious hypoglycemia (mean 0.5%, range 0.1–1.3% of time spent < 54 mg/dL), and 72 youth (30.0%) experienced a long duration of clinically serious hypoglycemia (mean 4.7%, range 1.2–14.6% of time spent < 54 mg/dL).

Table 3 displays the sequentially adjusted results of logistic regression models representing the odds ratio (OR) associated with long duration of hypoglycemia versus short duration or no hypoglycemia. In the fully adjusted model (Model 3), a long duration of clinical hypoglycemia was associated with increasing age (OR 1.32, 95% CI 1.01, 1.72) and decreasing HbA1c (OR 0.50, 95% CI 0.37, 0.67). Long duration of clinically serious hypoglycemia was associated with increasing age (OR 1.35, 95% CI 1.02, 1.77), decreasing HbA1c (OR 0.52, 95% CI 0.38, 0.70), and pump use (OR = 2.17, 95% CI 1.06, 4.44). Sex, race/ethnicity, type 1 diabetes duration, BMIz, fear of hypoglycemia (Maintain High BG, Worry/Helplessness subscales) and type 1 diabetes adherence were not significantly associated with hypoglycemia. The inverse relationship between duration of clinical and clinically serious hypoglycemia with concurrently measured HbA1c is presented in Figure 1. Across the range of HbA1c from approximately 8–13% [64–119 mmol], each 1% lower HbA1c was associated with 8.7 more minutes per day of clinical hypoglycemia and 7.0 more minutes per day of clinically serious hypoglycemia.

Conclusions

Using data from 7-days of blinded CGM wear time, this study demonstrates that hypoglycemia is common among youth with elevated HbA1c, including clinically serious hypoglycemia (< 54 mg/dL). Despite the mean HbA1c of 9.6%, nearly four out of every five adolescents experienced clinical episodes of hypoglycemia < 70 mg/dL during the 7-day period and more than half experienced clinically significant episodes < 54 mg/dL. To our knowledge, there are few other studies available of adolescents with similar HbA1c distribution for comparison (i.e. 66% with HbA1c $> 9.0\%$ [75 mmol/mol]) (13).

Measures of the incidence and duration of hypoglycemia was greater during the daytime than overnight. The interpretation of this finding must consider that a higher number of hours allocated to day versus night, and despite reaching statistical significance, the small magnitude of difference in percentage of time spent in hypoglycemia are not likely clinically significant. However, the difference in incidence of both clinical and clinically serious hypoglycemia may reflect challenges of insulin dosing that adolescents experience with regards to waking activities, such as erratic food intake, bolusing or exercise (1, 22); these may be more pronounced in youth with type 1 diabetes who have elevated HbA1c. This contrasts with reports of hypoglycemia occurring most frequently during sleep among samples with lower mean HbA1c (4, 5, 11, 23, 24). These data therefore may help inform clinical advice on how to prevent hypoglycemia, where patterns in incidence suggest that education and support may be maximally effective if it is focused on challenges that arise during waking hours, including insulin adjustments for meals and physical activity. Given the benefits of reducing nocturnal hypoglycemia, the data are somewhat reassuring as minimal overnight hypoglycemia was documented in the present study.

Results from this study suggest that adolescents with type 1 diabetes struggle with hypoglycemia independent of race/ethnicity, sex, disease duration, and adherence. Youth who reported using a pump versus MDI had more than twice the odds of experiencing clinically serious hypoglycemia, but not clinical hypoglycemia. This is in contrast to multiple studies of adolescents showing pump therapy can reduce the risk of severe hypoglycemia (25, 26). It may be that pump users are more likely to experience *non-severe* hypoglycemia, but less likely to experience *severe* hypoglycemia. Pump use may also facilitate the administration of poorly considered doses, including large boluses associated with frustration in response to hyperglycemia, especially in those with elevated HbA1c. More studies are warranted to understand the association between pump use and hypoglycemia, as well as the specific behaviors that may mediate it.

Fear of hypoglycemia was not associated with duration of hypoglycemia nor the frequency of episodes. Previous research has shown that fear of hypoglycemia, aversive behaviors, and anxiety have been specifically linked to episodes of severe hypoglycemic episodes (27, 28). One possible explanation for the lack of association in this sample may be related to the lack of severe hypoglycemia (i.e. episodes involving the loss of consciousness or requiring the help of others) that occurred during the week in which CGMs were worn. The association with fear of hypoglycemia may be attenuated with milder experiences of hypoglycemia captured by CGM wear.

One of the findings of the present study is that the duration of clinical and clinically serious hypoglycemia was inversely related to HbA1c. Importantly, the adolescents in this study were eligible for the study because their HbA1c levels were within the range of 8–13% [64–119 mmol], indicating that longer durations of hypoglycemia may be related to lower HbA1c in an above-target HbA1c range. Older studies focusing on severe hypoglycemia, defined by loss of consciousness, report a similar inverse relationship between severe hypoglycemia and HbA1c (4, 5), although other literature findings do not (6–8, 25). It may be that the non-severe hypoglycemia, as measured in the current study, represents a distinct phenomenon from the severe hypoglycemia that includes loss of consciousness and seizure.

It has been proposed that such non-severe hypoglycemia may initiate a cycle of excess carbohydrate consumption in response to hypoglycemia, glycemic overcorrection and hyperglycemia, and the need for additional insulin, which may contribute to glucose variability, obesity, and increased HbA1c (29–33). To address the relationship between hypoglycemia and glycemic variability, adolescents could benefit from education and support surrounding avoiding the overtreatment of hypoglycemia alongside approaches towards prevention of hypoglycemia altogether. For example, this education could include strategies on how to avoid the disinhibited eating and tolerate the distress that individuals with type 1 diabetes report to be common in response to episodes of hypoglycemia (34–36).

The inverse association between hypoglycemia and HbA1c within the 8–13% range found in the present study may also give imperative for the increased use of diabetes tools and technology to help adolescents more effectively monitor and prevent hypoglycemia, thereby facilitating efforts to obtain glycemic control. For example, real-time CGM with alarms may expose blood glucose trends more readily and help adolescents and their parents to preempt hypoglycemic episodes. CGM use in the United States adolescent population has increased from 3% in 2011 to 17% in 2016, and is associated with lower HbA1c among pediatric populations (13). With Federal Drug Administration approval for non-adjunctive use and newer systems that do not require calibration, device uptake is likely to increase even more in the future (13, 37), especially if access is increased to those with public insurance (38). Moreover, automated insulin technology including hybrid closed loop systems and predictive low glucose suspend features may be more effective in directly preventing hypoglycemia, while simultaneously decreasing some of the burden of day-to-day glucose management. Future efforts should be made to increase availability, facilitate access, and encourage adoption of current and emerging diabetes technology for adolescents with suboptimal glycemic control, a population in which these tools may be especially helpful to concurrently prevent hypoglycemia while also potentially improving HbA1c and decreasing glucose variability.

To our knowledge, this study represents one of the first analyses of blinded CGM data from adolescents with elevated HbA1c, a subgroup with increased risk for both short- and long-term complications of type 1 diabetes (39). The findings demonstrate that similar to those with HbA1c levels <9.0% [75 mmol/mol], non-severe hypoglycemia is also prevalent in a population of individuals with HbA1c levels in the suboptimal range. This reinforces how CGM profiles may explore critical information for optimizing type 1 diabetes care that extends beyond average glycemic control as measured by HbA1c (15). More specifically, CGM use may allow for the routine assessment of both hyper- and hypoglycemic excursions to develop and practice more effective, personalized diabetes self-management strategies.

The current study should be considered in the context of its limitations and strengths. The analysis was cross-sectional and thus cannot be used to infer causal associations with hypoglycemia. Future studies are needed to assess the temporality of significant associations, potential mediators, and how within-person changes in HbA1c may be associated with hypoglycemia. Youth wore blinded CGM for 1 week, which may not be long enough to capture the full range of meaningful patterns or how non-severe hypoglycemia episodes are related to severe episodes (21). Finally, the times of day used to infer sleep and

waking patterns may not be appropriate for adolescents, who can have erratic sleep schedules. However, the study also has several strengths, including the use of a novel dataset representing a high-risk group of adolescents with type 1 diabetes, objective measurement and characterization of an important diabetes outcome— including the incidence and duration of hypoglycemia— that has not been well-described in this age-range, and availability of multiple demographic, clinical, and behavioral variables as potential correlates of hypoglycemia.

In conclusion, the results of this study demonstrate that non-severe hypoglycemia is prevalent among adolescents with type 1 diabetes and suboptimal glycemic control. Education and anticipatory guidance to limit the frequency and duration of hypoglycemia episodes should remain a central part of care in adolescents with type 1 diabetes. In addition, HbA1c should be used in combination with other metrics of dysglycemia, including objective measurement of hypoglycemia from CGMs, to tailor approaches for hypoglycemia prevention and management (1, 40). Adolescents may also benefit from increased use of real-time CGM for increased monitoring capacity and automated insulin dosing algorithms to prevent hypoglycemia. Behavioral support for optimal use of this type of technology will also be necessary in order to achieve the goal of improving glycemic control as measured by both HbA1c and glycemic variability.

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Duration of Hypoglycemia by Hemoglobin A1c in the FLEX Trial (n=233)

Figure 1: Average Minutes per Day (24-hour period) of Clinical Hypoglycemia and Clinically Serious Hypoglycemia Among Youth with Type 1 Diabetes in the FLEX Trial (n=233), Plotted by Hemoglobin A1c.

Note: Youth with HbA1c <8.0% or >13.0% at study baseline had previously met eligibility criteria for FLEX at recruitment screening. Participants were not excluded based on baseline HbA1c measures.

Table 1.

Demographic and Clinical Characteristics of FLEX Participants (n=233), Stratified by Duration of Clinical and Clinically Serious Hypoglycemia^a

	All (n=233)	Clinical Hypoglycemia (duration of time ≥ 70 mg/dL and ≥ 54 mg/dL) ^b			Clinically Serious Hypoglycemia (duration of time ≥ 54 mg/dL) ^c		
		None/Short duration (n=135)	Long duration (n=98)	P-value	None/Short duration (n=161)	Long duration (n=72)	P-value
Demographic and Clinical Characteristics, mean (SD) or n (%)							
Age (years)	14.9 (1.3)	14.8 (1.1)	15.0 (1.3)	0.137	14.7 (1.1)	15.1 (1.2)	0.025
Female sex	116 (49.8)	66 (48.9)	50 (51.0)	0.748	80 (49.7)	36 (50.0)	0.965
Race and Ethnicity				0.527 [*]			0.962
Non-Hispanic white	177 (76.0)	105 (77.8)	72 (73.5)		121 (75.2)	56 (77.8)	
Black	11 (4.7)	6 (4.4)	5 (5.1)		8 (5.0)	3 (4.2)	
Hispanic	32 (13.7)	19 (14.1)	13 (13.3)		22 (13.7)	10 (13.9)	
Other	13 (5.6)	5 (3.7)	8 (8.2)				
Public Health Insurance	163 (70.0)	101 (74.8)	62 (63.3)	0.058	119 (73.9)	44 (61.1)	0.048
Single adult home	30 (13.2)	18 (13.5)	12 (12.6)	0.842	19 (12.1)	11 (15.5)	0.483
Duration of diabetes (years)	6.4 (3.7)	6.4 (3.8)	6.6 (3.6)	0.685	6.4 (3.7)	6.6 (3.8)	0.611
HbA1c, %	9.6 (1.2)	9.9 (1.3)	9.2 (1.1)	<0.001	9.8 (1.3)	9.2 (1.0)	<0.001
HbA1c $>9.0\%$ [75 mmol/mol]	156 (66.1)	103 (76.3)	53 (54.1)	<0.001	116 (72.1)	40 (55.6)	0.013
BMI z-score	0.72 (0.91)	0.74 (0.90)	0.68 (0.94)	0.610	0.68 (0.91)	0.80 (0.92)	0.360
Weight Status				0.994			0.672
Under- or normal weight	143 (61.4)	83 (61.5)	60 (61.2)		101 (62.7)	42 (58.3)	
Overweight	55 (23.6)	32 (23.7)	23 (23.5)		38 (23.6)	17 (23.6)	
Obese	35 (15.0)	20 (14.8)	15 (15.3)		22 (13.7)	13 (18.1)	
Insulin Regimen				0.615			0.367
Multiple daily injection	68 (29.3)	41 (30.6)	27 (27.6)		44 (27.5)	24 (33.3)	
Pump	164 (70.7)	93 (69.4)	71 (72.5)		116 (72.5)	48 (66.7)	
Used CGM in past month	66 (28.3)	38 (28.2)	28 (28.6)	0.944	47 (29.2)	19 (26.4)	0.661
Episode of self-reported severe hypoglycemia in the past 6 months	17 (6.6)	13 (8.2)	4 (4.0)	0.302	13 (7.0)	4 (5.6)	0.677

		Clinical Hypoglycemia (duration of time 70 mg/dL and >54 mg/dL) ^b			Clinically Serious Hypoglycemia (duration of time >54 mg/dL) ^c		
	All (n=233)	None/Short duration (n=135)	Long duration (n=98)	P-value	None/Short duration (n=161)	Long duration (n=72)	P-value
Cognitive and Behavioral Characteristics							
Diabetes self-management ^c	55.1 (11.6)	55.3 (11.5)	55.9 (11.8)	0.836	55.6 (11.2)	54.1 (12.2)	0.387
Fear of hypoglycemia, Maintain High BG ^d	1.18 (0.87)	1.2 (0.89)	1.18 (0.86)	0.969	1.19 (0.92)	1.13 (0.74)	0.596
Fear of hypoglycemia, Helplessness/Worry ^d	1.11 (0.55)	1.12 (0.60)	1.10 (0.48)	0.735	1.10 (0.60)	1.14 (0.42)	0.615
Fear of hypoglycemia, Worry About Negative Social Consequences ^d	1.09 (0.73)	1.09 (0.77)	1.10 (0.67)	0.964	1.06 (0.76)	1.17 (0.63)	0.231

Data are mean (SD), n (%) or median (Q1-Q3). P-values from chi-square and t-tests (Fischer's Exact and Wilcoxon-Mann-Whitney where appropriate).

* Fischer's Exact Test was used for comparisons where cells had n<10.

^a Clinical hypoglycemia defined as duration of time <70 mg/dL and >54 mg/dL over 7-day period of blinded continuous glucose monitor wear time. None (n=37); mean 0%, range 0.0–0.0%. Short duration (n=98); mean 0.8%, range 0.04–1.8%; Long duration (n=98); mean 4.4%, range 1.8–17.4%.

^b Clinically serious hypoglycemia defined as duration of time <54 mg/dL over 7-day period of blinded continuous glucose monitor wear time. None (n=90); mean 0.0%, range 0.0–0.0%. Short duration (n=71); mean 0.5%, range 0.1–1.3%; Long duration (n=72); mean 4.7%, range 1.2–14.6%.

^c Diabetes adherence during the previous three months was measured by the Diabetes Self-Management Profile – Self Report (DSMP-SR) score; higher score indicates more diabetes self-management behaviors.

^d Fear of hypoglycemia was assessed by the Hypoglycemia Fear Survey (HFS) and measured in three domains: behaviors used to keep blood glucose high to prevent hypoglycemia ('Maintain High BG'), worry about helplessness ('Worry/Helplessness'), and worry about social consequences associated with hypoglycemia ('Worry/Social Consequences'); higher scores indicate higher levels of fear.

Abbreviations: HbA1c = Hemoglobin A1c. BMI z-score = Body Mass Index z-score. CGM = continuous glucose monitoring

Table 2.

Measures of Clinical Hypoglycemia, Clinically Serious Hypoglycemia, and Other CGM-Derived Measures from Youth with Type 1 Diabetes in the FLEX Trial (n=233), Stratified by Day and Night

	Overall	Day ^c	Night ^c	p-value
Hypoglycemia Incidence				
Experienced 1 or more hypoglycemic episodes <70 mg/dL lasting 15 or more minutes in the 7-days, n (%)	184 (79.0)	170 (73.0)	125 (53.7)	<0.001
Number of hypoglycemic episodes <70 mg/dL lasting 15 or more minutes, median (Q1, Q3; range)	3 (1, 6; 0–27)	2 (0, 5; 0–23)	1 (0–2; 0–9)	<0.001
Experienced 1 or more hypoglycemic episodes ≤54 mg/dL lasting 15 or more minutes in the 7-days, n (%)	129 (55.4)	112 (48.1)	83 (35.6)	<0.001
Number of hypoglycemic episodes ≤54 mg/dL lasting 15 or more minutes, median (Q1, Q3; range)	1 (0–2; 0–20)	0 (0–2; 0–16)	0 (0–1; 0–6)	<0.001
Hypoglycemia Duration				
<i>Clinical Hypoglycemia (< 70 mg/dL and > 54 mg/dL)^a</i>				
Percent of time (%), median (IQR)	1.5 (3.1)	1.0 (2.7)	1.1 (4.1)	<0.001
Duration per day (min), median (Q1, Q3; range)	21.9 (3.6, 47.9; 0.0–250.2)	--	--	--
<i>Clinical Hypoglycemia (< 54 mg/dL)^b</i>				
Percent of time (%), median (IQR)	0.3 (2.2)	0.2 (1.4)	0.0 (2.6)	<0.001
Duration per day (min), median (Q1, Q3; range)	4.3 (0, 31.5; 0.0–209.7)	--	--	--
Hyperglycemia, Mean Glucose Exposure, and Glycemic Variability				
Median CGM measure, mg/dL, mean (SD)	213.7 (44.4)	221.2 (48.0)	192.9 (55.3)	<0.001
Percent of time in range (70–180 mg/dL) (%), mean (SD)	34.7 (13.6)	33.3 (14.0)	28.7 (18.4)	<0.001
Percent of time > 180 mg/dL (%), mean (SD)	61.5 (15.8)	63.7 (15.9)	55.0 (22.0)	<0.001
Percent of time > 250 mg/dL (%), mean (SD)	35.8 (16.3)	38.3 (17.2)	28.4 (19.7)	<0.001
Standard Deviation mean (SD)	85.7 (14.8)	85.7 (14.9)	74.6 (20.4)	<0.001
Coefficient of variation ^b (%), mean (SD)	40.0 (7.7)	38.8 (7.4)	38.8 (11.9)	0.903

p-values are from paired t-tests or chi-square tests comparing day versus night.

^aClinical hypoglycemia defined as duration of time <70 mg/dL and ≥54 mg/dL over 7-day period of blinded continuous glucose monitor wear time.

^bClinically serious hypoglycemia defined as duration of time <54 mg/dL over 7-day period of blinded continuous glucose monitor wear time.

^cDay defined as 6:00 AM–11:59 PM. Night defined as 12:00 AM–5:59 AM.

Abbreviations: SD = Standard Deviation. IQR = interquartile range CGM = continuous glucose monitoring

Table 3:

Unadjusted and Sequentially Adjusted Results of Logistic Regression Models Representing the Odds Ratio (OR) Associated with Long Duration of Hypoglycemia Versus Short Duration or No Hypoglycemia in Youth with Type 1 Diabetes (n=233)^{*}

	Clinical Hypoglycemia (duration of time 70 mg/dL and >54 mg/dL) ^a			Clinically Serious Hypoglycemia (duration of time 54 mg/dL) ^b		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Female sex	1.14 (0.67, 1.93)	1.14 (0.65, 2.00)	1.24 (0.69, 2.22)	1.02 (0.58, 1.81)	0.99 (0.65, 1.80)	0.98 (0.53, 1.81)
Age (1-year increase)	1.20 (0.95, 1.52)	1.32 (1.02, 1.71)	1.32 (1.01, 1.72)	1.34 (1.04, 1.71)	1.40 (1.07, 1.84)	1.35 (1.02, 1.77)
Nonwhite race/ethnicity (versus non-Hispanic White race/ethnicity) ^c	1.31 (0.71, 2.43)	1.56 (0.81, 3.03)	1.56 (0.79, 3.08)	0.89 (0.45, 1.75)	0.91 (0.45, 1.86)	0.97 (0.47, 2.01)
Diabetes duration (1-year increase)	--	1.01 (0.94, 1.09)	1.01 (0.94, 1.09)	--	1.03 (0.95, 1.11)	1.03 (0.95, 1.120)
Insulin Regimen (pump versus multiple daily injections)	--	1.26 (0.65, 2.44)	1.21 (0.62, 2.39)	--	2.01 (0.99, 4.05)	2.17 (1.06, 4.44)
Hemoglobin A1c (1% increase)	--	0.55 (0.42, 0.72)	0.50 (0.37, 0.67)	--	0.55 (0.41, 0.74)	0.52 (0.38, 0.71)
Body mass index z-score (1-unit increase)	--	0.90 (0.66, 1.23)	0.90 (0.66, 1.25)	--	1.14 (0.81, 1.59)	1.14 (0.81, 1.60)
Diabetes Adherence ^d (1-unit increase in DSMP-SR score)	--	--	0.98 (0.96, 1.01)	--	--	0.98 (0.95, 1.01)
Fear of Hypoglycemia- Maintain High BG ^e (1-unit increase in HFS score)	--	--	1.08 (0.77, 1.53)	--	--	0.90 (0.62, 1.32)
Fear of Hypoglycemia- Helplessness/Worry ^e (1-unit increase in HFS score)	--	--	0.81 (0.47, 1.42)	--	--	1.25 (0.70, 2.23)

^aClinical hypoglycemia defined as duration of time <70 mg/dL and 54 mg/dL over 7-day period of blinded continuous glucose monitor wear time. Long duration (n= 98) versus short duration or no hypoglycemia (n=135).

^bClinically serious hypoglycemia defined as duration of time <54 mg/dL over 7-day period of blinded continuous glucose monitor wear time. Long duration (n= 72) versus short duration or no hypoglycemia (n=161).

^cNonwhite defined as all groups that did not identify as non-Hispanic white, including non-Hispanic Black, Black, Asian/Pacific Islander, Native American, other, or unknown.

^dDiabetes adherence during the previous three months was measured by the Diabetes Self-Management Profile – Self Report (DSMP-SR) score.

^eFear of hypoglycemia was assessed by the Hypoglycemia Fear Survey (HFS). The Worry about Social Consequences subscale was dropped due to collinearity.

^{*} Sequentially Adjusted Models:

Model 1: Demographic factors (age, sex, race)

Model 2: Clinical factors (type 1 diabetes duration, insulin regimen, HbA1c, BMIz)

Model 3: Cognitive/behavioral factors (diabetes adherence, LBS)