HHS Public Access

Author manuscript

Pediatr Diabetes. Author manuscript; available in PMC 2022 June 08.

Published in final edited form as:

Pediatr Diabetes. 2020 December ; 21(8): 1475–1484. doi:10.1111/pedi.13132.

Dietary intake on days with and without hypoglycemia in youth with type 1 diabetes: The Flexible Lifestyle Empowering Change trial

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Abstract

Objective—To address a common perception that hypoglycemia is associated with increased dietary intake, we examined calorie and carbohydrate consumption on days with and without hypoglycemia among adolescents with type 1 diabetes (T1D).

Methods—Days (N=274) with 24-hour dietary recalls and continuous glucose monitoring were available for 122 adolescents with T1D in the Flexible Lifestyle Empowering Change trial (age 13–16 years, diabetes duration >1 year, hemoglobin A1c 8–13%). Days with no hypoglycemia, clinical hypoglycemia (54–69 mg/dL) or clinically serious hypoglycemia (<54 mg/dL) were further split into night- (12–5:59 AM) and day (6 AM–11:59 PM). Mixed models tested whether intake of calories or carbohydrates was greater on days with than without hypoglycemia.

Results—Fifty-nine percent, 23% and 18% of days had no hypoglycemia, clinical hypoglycemia and clinically serious hypoglycemia, respectively. Intake of calories and carbohydrates was not statistically significantly different on days with clinical hypoglycemia (57.2 kcal [95% CI −126.7, 241.5]; 12.6 g carbohydrate [95% CI −12.7, 38.0]) or clinically serious hypoglycemia (−74.0 kcal [95% CI −285.9, 137.9]; (−7.8 g carbohydrate [95% CI −36.8, 21.1]), compared to days without hypoglycemia. Differences by day and night were not statistically significant.

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Contributors: DI 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. DI, JC, ARK and EMD designed the analyses. DI conducted the analyses with the oversight of JC. DI drafted the initial manuscript. All authors provided critical review and approved the final manuscript.

Conclusions—Among adolescents with T1D, daily intake of calories and carbohydrates did not differ on days with and without hypoglycemia. It is possible that hypoglycemic episodes is caused by undereating relative to insulin dosing, followed by overeating, leading to a net neutral difference. Given the post-hoc nature of these analyses, larger studies should be designed to prospectively test the hypoglycemia-diet relationship.

Keywords

Diabetes Mellitus; Type 1; Hypoglycemia; Dietary Intake; Nutrition; Continuous Glucose Monitoring

Introduction

Managing hypoglycemia, including prevention and treatment, is a known challenge for adolescents with type 1 diabetes (T1D). All episodes of hypoglycemia require individuals to ingest additional rescue carbohydrates. Moreover, there is a clinical perception in the T1D literature that a cycle of restriction and binge eating leads to hypo- and subsequent hyperglycemia,[1] as acute and intense hunger may lead to overcorrection with excess carbohydrate.[2] As such, both fear of hypoglycemia and hypoglycemia-induced binge eating[3] may interfere with efforts to maintain euglycemia.[4] While clinical practice guidelines recommend treatment of hypoglycemia with glucose,[5] recent studies hypothesize that recurrent hypoglycemia, possibly triggered by dietary restraint,[6–8] is associated with intense hunger and permission to eat forbidden sugary foods, which may become habitual.[1] The resultant overeating, guilt, restriction, and possibly more episodes of hypoglycemia, may create a self-perpetuating cycle of disordered eating behaviors resembling binge eating disorder and bulimia.[2] This proposed cycle is thought to disrupt physiological hunger cues and result in a net surplus of calories as restriction and excess intake continue. Excess dietary intake is also posited to increase the amount of insulin that is administered, which in the long-term may lead to weight gain.[2,7–14] While one survey-based study found that 88% of adolescents with T1D endorsed overeating “once in a while” in response to perceived hypoglycemia,[15] to our knowledge, the notion of excess dietary intake in response to hypoglycemia has not been systematically tested.

We previously showed that among 98 participants in the Flexible Lifestyle Empowering Change clinical trial (FLEX, ClinicalTrials.gov identifier: NCT01286350), greater than 80% of participants had at least one episode of hypoglycemia over seven days of continuous glucose monitor (CGM) wear.[16] We further demonstrated in a qualitative study that youth with T1D universally endorsed impulsive and uncontrollable eating during episodes of hypoglycemia.[17] However, few studies have directly examined specific dietary responses to hypoglycemia in adolescents with T1D. Therefore, the objective of this study was to test the hypothesis that there is excess daily intake of calories and carbohydrates on days when hypoglycemia occurs in a sample of adolescents with T1D in the FLEX trial. We further aimed to describe the hypothesized hypoglycemia-diet relationship according to whether hypoglycemia occurred during the day or at night.

As our research question was whether short-term daily intake of calories and carbohydrates was greater on days with than on days without hypoglycemia, as opposed to usual (long-term) intake, we expected that there would be an absolute difference in calorie and carbohydrate intake, but no difference in the percent of carbohydrates consumed (i.e., no difference in diet quality), given that a person could have reasonable diet quality, but still overconsume carbohydrates on days with hypoglycemia. From a dietary patterns perspective, changes in intake of discretionary calories (i.e., additional sugars) specifically on days with hypoglycemia may therefore not alter the overall quality of the diet, but could still have long-term impacts on glycemia and possibly weight. Furthermore, given the heterogeneity of causes underlying hypoglycemia (e.g., insulin misdosing, physical activity, changes in food intake, etc.), frequency of hypoglycemia is not necessarily an indicator of poor diet quality.

Research Design and Methods

Study Sample

The study design and main results of FLEX have been described elsewhere.[18,19] Briefly, FLEX was an 18-month randomized clinical trial testing the effect of an adaptive intervention with behavioral and problem-solving skills for youth with T1D (intervention arm) compared with usual diabetes care (control arm), on hemoglobin A1c (HbA1c, primary outcome), cardiovascular disease risk factors, health-related quality of life, and cost effectiveness. Given that FLEX was not a dietary intervention, general recommendations for a healthy diet were consistent across the intervention and control groups. Eligible participants were youth aged 13–16 years with T1D 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.[18] The adolescent age for inclusion of 13–16 years allowed the study participants to complete the 24-hr recalls themselves, but if adolescents had questions about how food was prepared, the caregiver could provide clarification.

Eligibility criteria were based on most recent point-of-care HbA1c measures in medical records (most recent HbA1c 8.0–13.0% [64–119 mmol/mol], measured within the past year). Youth meeting the clinical criteria according to medical record data were targeted for a two-step recruitment process and enrolled in the trial, after which time they had the baseline visit. 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 at Chapel Hill.[18,19] The current analyses used baseline and 6-month follow-up data from a subset of the 258 adolescents from the FLEX trial who also participated in the ancillary CGM study. 24-hr dietary recalls were collected only for participants in the ancillary CGM study.

Ancillary CGM Study

Of the 258 adolescents with T1D who were enrolled in FLEX, n=134 participated in the ancillary CGM study. CGM data were collected at baseline, 6-months, and 18-months of the trial, but given that diet data were collected at baseline and 6-months, the present analyses

utilized only baseline and 6-month CGM and diet data. Participants who did or did not participate in the ancillary study did not differ with respect to study group membership (49.2% of those included and 50.8% of those excluded were assigned to intervention, while 54.7% of those included and 45.3% of those excluded were assigned to control; p=0.38).

116 participants did not complete a dietary recall at baseline or 6-month follow-up, either because they completed baseline data collection before funding for the ancillary CGM study was received (n=95 participants), refused participation (n=4 participants), could not be scheduled/reached for a dietary recall (n=25 participants), and for other reasons (n=4 participants). Therefore, 142 participants completed 391 24-hour dietary recalls at baseline and 6-month follow-up (either or both). Each participant completed between 1–4 diet recalls (1–2 recalls per time point). Fifty-five dietary recalls were excluded because CGM data were missing on the day of the recall. Another 60 dietary recalls were excluded from days on which >2 hours of CGM data were missing. Two observations had outlier values for calories (>3 x IQR above quartile 3) and were removed from analyses. The final analytic sample consisted of 274 days on which concurrent CGM data and dietary recall data were available for 122 adolescents. Of those participants included in analyses, at baseline, 40 participants had 1 recall and 64 participants had 2 recalls; at 6-month follow-up, 32 participants had 1 recall and 37 participants had 2 recalls.

Measures

Laboratory data—At all study timepoints, including study entry (i.e., the baseline visit), blood was drawn on-site during study visits. HbA1c assays were conducted at a central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA, USA). 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.[20]

Questionnaires—Standardized questionnaires were used to collect self-reported data including age, sex, race/ethnicity, duration of T1D, and insulin delivery method (pump versus multiple daily injections [MDI]). Self-reported race/ethnicity was classified as non-Hispanic white, Hispanic, Non-Hispanic Black, and other including Asian/Pacific Islander, Native American, or unknown.

Continuous Glucose Monitoring Measures—A blinded CGM [iPro®2 Professional CGM; Medtronic Diabetes, Northridge, CA; median absolute relative difference: 11.1%][21] was worn for a 7-day period to measure interstitial glucose levels in real time throughout the day and night. At the baseline and 6-month visits, 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 International Hypoglycemia Study Group values.[22,23]

Physical Activity—The validated Previous Day Physical Activity Recall[24,25] was administered via telephone concurrently with 24-hour dietary recalls by UNC NIH/NIDDK Nutrition Obesity Research Center (NORC) staff. Interviewers queried the primary activity and its intensity during each half-hour time block during the previous day. In the current analyses, intensity levels were coded as the daily number of hours during which participants engaged in moderate or vigorous physical activity based on prior associations with reduced cardiometabolic risk factors in youth.[26,27] Intensity was also used to code sedentary time, which was expressed as the number of hours spent watching television or using electronic media. Television time was not retained in inferential models due to collinearity with electronic media.

Exposures

We used standardized definitions of hypoglycemia set forth by position statements of the International Hypoglycemia Study Group from the International Society of Pediatric and Adolescent Diabetes.[23,28,29] The primary exposure was hypoglycemia categorized as a three-level variable: 1) days with no episodes of hypoglycemia (<70 mg/dL) lasting ≥15 minutes; 2) days with at least one episode of clinical hypoglycemia (54–69 mg/dL) lasting ≥15 minutes, but no episodes of clinically serious hypoglycemia (<54 mg/dL), although glucose could have dropped below 54, but stayed there less than 15 minutes; and 3) days with at least one episode of clinically serious hypoglycemia lasting ≥15 minutes. 24-hr diet recalls represented daily intake between 12:00 AM and 11:59 PM; therefore, CGM data were accordingly aligned with diet data, and were similarly coded as beginning at 12:00 AM and ending at 11:59 PM.

The three-level hypoglycemia variable was also calculated separately for night (12–5:59 AM) and day (6 AM–11:59 PM). Both night- and daytime hypoglycemia may have occurred in a single day—i.e., a single day may have had a clinically serious daytime episode and a clinical nighttime episode, and would be categorized as “clinically serious” overall and for daytime, but as “clinical” for nighttime.

Exploratory analyses used the alternate exposure variable of daily hypoglycemia duration. Due to the large number of days with zero duration of hypoglycemia, days were categorized into mutually exclusive categories: 1) days with 0% hypoglycemia duration (i.e., no readings <70 mg/dL), 2) days below the non-zero median duration of 2.98% time spent in hypoglycemia (range 0.05–2.98%), and 3) days above the non-zero median duration of 2.98% time spent in hypoglycemia (range 3.16–29.7%). Median duration was

computed using only days with non-zero hypoglycemia duration (i.e., days with at least one reading <70 mg/dL). Additional exploratory subgroup analyses separated the 3-level hypoglycemia exposure variable into weekdays and weekends. Weekdays and weekends were categorized according to whether or not at least one episode of clinical or clinically serious hypoglycemia lasting ≥15 minutes had occurred, similar to the primary exposure variable.

Outcomes

24-hour dietary recalls were administered via telephone by trained NORC staff using a multi-pass method.[30,31] Recalls were collected following a standard script on non-consecutive days and ideally included one weekday and one weekend day. Each day represents dietary intake between 12:00 AM and 11:59 PM. Nutrition Data System for Research Version 2014, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN[32] was used to derive nutrients associated with recalled foods and beverages. Daily calorie or carbohydrate (grams) intake were used as outcome variables for all analyses.

Statistical Power

Our final sample consisted of 274 days of concurrent CGM and 24-hour dietary recall data. The distribution of the primary exposure variable across combined baseline and 6-month follow-up timepoints was as follows: 59% (n=163) of days had no episodes of hypoglycemia lasting ≥15 minutes, 23% (n=62) of days had at least one episode of clinical hypoglycemia, and 18% (n=49) of days had at least one episode of clinically serious hypoglycemia. Based on these sample sizes, in a three-group comparison we had 80% power to detect an effect when the difference (effect size) between the highest and lowest group was as small as d=0.40. This corresponds to a difference in outcome of 286 calories (kcal), 41 grams of carbohydrates, or 3.7% calories from carbohydrates. For a two-group comparison, we estimated that we had 80% power to detect an effect of d=0.46 between the “no hypoglycemia” days and the “clinically serious hypoglycemia” days. This corresponds to a difference in outcome of 329 kcal, 47 grams of carbohydrates, or 4.3% calories from carbohydrates. This statistical power is adequate to detect medium effects in the sample, but power is low if the effect of hypoglycemia on diet is small.[33]

Statistical Analysis

Descriptive data in Tables 2 and 3 were not subjected to statistical testing due to non-independence of repeated measures (i.e., participants could have contributed up to 4 days of data). Linear mixed models accounting for repeated measures tested the hypothesis that intake of calories and grams of carbohydrates was greater on days with clinical or clinically serious hypoglycemia compared to days without hypoglycemia. Separate models were used for calories and carbohydrates, modeled as a function of daily hypoglycemia category. Sequential models were constructed as follows. Model 1: unadjusted with repeated measures of participant ID, clinical site (Colorado or Ohio), and recall number (1–4); Model 2: adjusted for study design variables (randomization assignment [intervention or control] and timepoint [baseline or follow-up]); Model 3: further adjusted for potential demographic confounders (age, sex, and race/ethnicity [non-Hispanic white or Other]);

and Model 4: further adjusted for potential clinical confounders (diabetes duration, insulin regimen [pump or multiple daily injection], HbA1c, and physical activity). All adjusted models (Models 2–4) used random effects to account for within-subject correlation within and across timepoints.

Exploratory analyses utilized the alternate exposure of hypoglycemia duration, to test the hypothesis that daily intake of calories and carbohydrates was greater on days with hypoglycemia duration above or below the median duration, compared to days with 0% duration. Additional exploratory subgroup analyses tested the 3-level hypoglycemia outcome (days with no hypoglycemia, clinical hypoglycemia, or clinically serious hypoglycemia) separately by weekdays and weekend days. We conducted sensitivity analyses to ensure that the proportion of days with no hypoglycemia, clinical hypoglycemia, or clinically serious hypoglycemia was not substantively different among participants who provided CGM data, with and without at least one dietary recall. We also tested whether there were statistically significant group (intervention vs. control), timepoint (baseline vs. follow-up), or interacted group by timepoint effects for calories or carbohydrates. A p-value of < 0.05 was considered statistically significant. Analyses were conducted using SAS, version 9.4.

Results

Participants contributed between 1–4 days of concurrent 24-hour dietary recalls and CGM data. Thirty (24.6%) participants had one recall, 50 (40.9%) participants had 2 recalls, 24 (19.7%) participants had 3 recalls, and 18 (14.8%) participants had 4 recalls. Of the 274 dietary recalls, 168 (61.3%) were obtained at baseline, and 106 (38.7%) were obtained at the 6-month follow-up.

Table 1 presents the characteristics of the study sample at baseline. Participants (n=122) were 79% non-Hispanic white and 54% female, had a mean age of 14.8 ± 1.1 years, diabetes duration of 6.4 ± 3.7 years, HbA1c of 9.3 ± 1.1% [78 ± 12 mmol/mol], and BMI z-score of 0.71 ± 0.90. Participants excluded from analyses due to missing diet or CGM data were not statistically significantly different from those included with regards to age, sex, race/ethnicity, diabetes duration, baseline BMI z-score, insulin dose, insulin regimen, clinic site, or intervention group, but had higher mean measures of HbA1c (9.8% ± 1.3 [84 ± 14.2 mmol/mol] vs. 9.3% ± 1.1 [78 ± 12 mmol/mol], p=0.0008) (Supplementary Table 1). Among days with CGM data that were excluded due to missing diet data, 62% of days included no episodes of hypoglycemia, 19% included at least one episode of clinical hypoglycemia, and 17% included at least one episode of clinically serious hypoglycemia. These proportions were not substantively different from days that were included in analyses.

Descriptive Analyses

Table 2 presents calorie and carbohydrate intake for the primary 3-level hypoglycemia exposure. Mean intake was 1798 ± 685 kcal and 221 ± 96 g carbohydrate on days with no hypoglycemia, 1804 ± 803 kcal and 224 ± 101 g carbohydrate on days with clinical hypoglycemia, and 1683 ± 707 kcal and 204 ± 92 g carbohydrate on days with clinically serious hypoglycemia. The percent of calories consumed as carbohydrate was 48.1 ±

9.9% on days with clinically serious hypoglycemia, 48.9 ± 8.2% on days with clinical hypoglycemia, and 47.8 ± 9.6% on days with no hypoglycemia.

Table 3 presents descriptive unadjusted results about days with day- and nighttime hypoglycemia. On average, intake was 1810 ± 692 kcal and 222 ± 98 g carbohydrate on days with no daytime hypoglycemia, 1798 ± 801 kcal and 220 ± 97 g carbohydrate on days with clinical daytime hypoglycemia, and 1598 ± 658 kcal and 195 ± 88 g carbohydrate on days with clinically serious daytime hypoglycemia. For nighttime hypoglycemia, mean intake was 1786 ± 711 kcal and 219 ± 96 g carbohydrate on days with no nighttime hypoglycemia, 1907 ± 856 kcal and 242 ± 118 g carbohydrate on days with clinical nighttime hypoglycemia, and 1638 ± 676 kcal and 196 ± 87 g carbohydrate on days with clinically serious nighttime hypoglycemia.

We used an alternate, exploratory variable for hypoglycemia in the form of daily hypoglycemia duration, for which 12.0% of days (n=33) had 0% hypoglycemia duration, 44.2% of days (n=121) had hypoglycemia duration below the median time, and 43.8% of days (n=120) had hypoglycemia duration above the median time (Supplementary Table 2). Mean intake was 1882 ± 695 kcal and 239 ± 107 g carbohydrate on days with no hypoglycemia duration, 1836 ± 739 kcal and 227 ± 98 g carbohydrate on days with hypoglycemia duration below the median, and 1694 ± 694 kcal and 203 ± 91 g carbohydrate on days with hypoglycemia duration above the median. Raw unadjusted mean calories and carbohydrates consumed on weekdays and weekend days with no hypoglycemia, clinical hypoglycemia, and clinically serious hypoglycemia are presented in Supplementary Table 3.

Sensitivity analyses revealed a statistically significant timepoint effect for daily carbohydrate intake. On average, 26 more g carbohydrate (95% CI 2, 51, p=0.03) were consumed at baseline compared to 6-month follow-up. The timepoint effect for carbohydrate intake was also statistically significant by day- and nighttime hypoglycemia. At baseline compared to 6-month follow-up, 30 more g carbohydrate (95% CI 8, 52, p=0.009) were consumed on days with daytime hypoglycemia, while 27 more g carbohydrate (95% CI 4, 49, p=0.02) were consumed on days with nighttime hypoglycemia.

Inferential Analyses

Table 4 presents the results of linear mixed models testing the primary hypothesis that daily intake of calories and carbohydrates is greater on days with clinical or clinically serious hypoglycemia compared to days with no hypoglycemia. All model results, both unadjusted and sequentially adjusted, yielded a statistically non-significant relationship between hypoglycemia and daily intake of calories or carbohydrates. The fully adjusted estimates were 57.2 kcal (95% CI −126.7, 241.5) and 12.6 g carbohydrate (95% CI −12.7, 38.0) for days with clinical hypoglycemia compared to days with no hypoglycemia; and −74.0 kcal (95% CI −285.9, 137.9) and −7.8 g carbohydrate (95% CI −36.8, 21.1) for days with clinically serious hypoglycemia compared to days with no hypoglycemia. The 3-group contrasts comparing days with no hypoglycemia, clinical hypoglycemia, and clinically serious hypoglycemia were p=0.56 for calories and p=0.43 for carbohydrates.

All linear mixed models for subgroup analyses by day- and nighttime hypoglycemia were not statistically significant for daily intake of calories or carbohydrates (Table 5). Unadjusted and sequentially adjusted exploratory analyses were not statistically significant, neither for hypoglycemia duration in association with daily calorie or carbohydrate intake (Supplementary Tables 4&5), nor for subgroup analyses split into weekday and weekend hypoglycemia (Supplementary Tables 6&7).

Discussion

In the current study, we did not find evidence to support our hypothesis that *daily intake* of calories and carbohydrates consumed would be greater on days with than without hypoglycemia. However, it should be noted that the point estimates (for the primary analysis and separately by day and night) were consistent in directionality, and trended towards increased calorie and carbohydrate intake on days with clinical hypoglycemia compared to days with no hypoglycemia; and reduced intake on days with clinically serious hypoglycemia compared to days with no hypoglycemia. The confidence intervals were quite wide (about 300–400 calories, and 50–60 grams of carbohydrates); thus, findings should be interpreted with caution. We found that generally, adolescents with T1D consumed approximately 48% of calories from carbohydrates, which is less than among adolescents without type 1 diabetes[34] and consistent with previous reports from the Type 1 Diabetes Exchange[34] and the SEARCH for Diabetes in Youth study.[35]

Exploratory subgroup analyses testing the relationship between hypoglycemia and dietary intake on weekdays and weekend days were not statistically significant; however, the directionality of estimates largely mirrored the primary analyses. Although these data should be interpreted with caution given the small sample size and wide confidence intervals, if a true population effect was missed, this may indicate the need to tailor dietary counseling and blood glucose management strategies to weekends and weekdays separately.

The consistent directionality in our point estimates, agnostic to hypoglycemia exposure variable specification, points to two potentially distinct phenomena. In the case of clinical hypoglycemia, it may be that adolescents do, in fact, overconsume to treat a low blood sugar. In this scenario, hypoglycemia would be the cause of excess food intake. Meanwhile, it is possible that clinically serious hypoglycemia is the consequence of reduced food intake for which meal-time insulin has not been adequately reduced. If both clinical and clinically serious hypoglycemia occurred on the same day, it is possible that this may have resulted in a net neutral intake. Patient education should emphasize both avoiding overcorrection of lows, and properly timing and calculating insulin doses for meals.

In the landmark Diabetes Complications and Control Trial (DCCT), a subset of individuals treated with intensive insulin therapy who gained weight were more likely to develop cardiovascular disease than their intensively treated counterparts who did not gain weight.[36] These data underscore that it is imperative to prevent excess weight gain in individuals with T1D, of which proper prevention and treatment of hypoglycemia may be one of multiple diabetes-specific components. Excess weight gain in the setting of T1D contributes to central obesity, dyslipidemia, elevated blood pressure, insulin resistance,[4,37,38] and increased

risk for cardiovascular disease.[4,38] Despite proposed metabolic processes[9] and behavioral challenges[39] unique to T1D with regard to weight management, studies have not directly examined the complex interplay between glycemic control, dietary intake, and weight status, which creates unique challenges for people with T1D to optimally manage their weight. To be maximally informative, future studies should consider these relationships longitudinally.

The current study should be considered in the context of its challenges and strengths. Analytically, we took advantage of the fact that this was not a diet intervention; we were therefore able to pool baseline and 6-month 24-hour dietary recall data to increase sample size and our power to detect statistically significant effects. While we were powered to detect a difference in outcome of 329 kcal and 47 grams of carbohydrates between the "no hypoglycemia" days and the "clinically serious hypoglycemia" days, the estimated differences were much smaller than those for which we were powered; therefore, it is possible that a true population effect was missed due to small sample size.

This study was not specifically designed to answer the posed questions of this post-hoc hypothesis generating analysis. The analysis was cross-sectional and thus cannot be used to infer causal associations. Further, this study design did not allow for temporal analysis of immediate response to each occasion of hypoglycemia due to imprecision in reporting of time of dietary intake in the 24-hour recalls; rather, we aimed to characterize dietary intake over the course of the full day. Therefore, a mixing of effects may have resulted from over-correction for hypoglycemia with excess intake in some instances, but systematically underconsuming and not reducing insulin leading to hypoglycemia at other times. Ideally, a granular meal-by-meal approach would assess real-time response to hypoglycemia, including the impact of insulin dosing for meals. The influence of insulin regimen may also be important; as we lacked power to conduct subgroup analyses, future studies should consider how this variable could influence treatment and prevention of hypoglycemia, as insulin pumps allow for greater flexibility to accommodate spontaneous changes in dietary intake.

In addition, 24-hour dietary recalls are memory-based, and therefore prone to recall errors; however, their use has been validated in children against food records,[40] which are not subject to recall bias as they are completed in real-time, and against doubly-labeled water, a gold-standard measure of energy expenditure.[41] Generalizability of this study is limited, given the narrow age range for inclusion of 13–16 years, and the restriction to adolescents in poor glycemic control (HbA1c 8–13%).

However, the study has additional strengths, including the use of a data set with adolescents with T1D in poor glycemic control and one-third with overweight or obesity —a demographic that is well-suited to the research question, as one would suspect that over-correcting for hypoglycemia would be more prominent among adolescents with elevated glycemia and overweight or obese BMI z-score than among those who co-manage glycemia and weight effectively. Further, the analyses account for potential confounding through sequential adjustment for multiple demographic and clinical covariates. Another strength of our approach is that it includes validated metrics of dietary intake (i.e., 24-hour recalls).[42] Although the DCCT established the links between intensive insulin therapy, weight gain,

and cardiovascular disease risk,[36] our study is novel in that no study has previously substantiated the anecdotal notion that daily hypoglycemia is associated with increased dietary intake.[36]

In conclusion, the results of this study counter the clinical perception that among youth with T1D, hypoglycemia is associated with significantly higher daily calorie and carbohydrate intake.[1,2,7] However, the directionality of estimates was remarkably consistent for both the primary outcome and for models divided into day and nighttime hypoglycemia, as well as for selected exploratory analyses. These results could be used to inform a larger longitudinal study of immediate dietary response to hypoglycemia, to establish whether a mismatch in insulin dose relative to dietary intake has occurred versus a low blood sugar that may be followed by excess intake. Our results highlight the importance of diabetes self-management education for fine-tuning meal-time insulin dosing practices in order to minimize the risk of hypoglycemia and avoid the dietary overcorrection of low blood glucose levels when they do occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The FLEX Study is indebted to the many youth and their families whose participation made this study possible. This study was supported by NIH/ NIDDK (1UC4DK101132) and Helmsley Charitable Trust. 24-hour recalls were obtained by the UNC Nutrition Obesity Research Center staff, funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number P30DK056350; MPI Mayer-Davis. DI is supported by the Global Cardiometabolic Disease training grant (National Heart, Lung, and Blood Institute of the National Institutes of Health) awarded to the Department of Nutrition at the University of North Carolina at Chapel Hill under Award Number HL129969. ARK is supported by the National Institute of Diabetes and Digestive and Kidney Disease of the National Institutes of Health under Award Number F30DK113728 and has received financial support from Novo Nordisk for travel to present data. DMM is supported by P30DK116074. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest: DMM has consulted for Abbott, Medtronic, the Helmsley Charitable Trust, Sanofi, Novo Nordisk, and Eli Lilly and has served on an advisory board for Insulet. EJM-D has consulted for Helmsley Charitable Trust. ARK has received travel support from Novo Nordisk to present data. All other authors declare no conflict of interest.

Role of the Funding Source:

The sponsor of this study was represented on the FLEX study steering committee (Christine M. Hunter, PhD, NIDDK) and as part of this committee contributed to the collaborative development of the FLEX study design and oversight of its execution.

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Table 1.

Baseline Demographic and Clinical Characteristics of FLEX Participants (n=122)

	Participants Included in Analyses
Demographic and Clinical Characteristics, mean (SD) or n (%)	
Age (years)	14.8 (1.1)
Female sex	66 (54.1)
Race and Ethnicity	
Non-Hispanic white	96 (78.7)
Other	26 (21.3)
Clinical site	
Colorado	67 (54.9)
Ohio	55 (45.1)
FLEX study group	
Intervention	59 (48.4)
Control	63 (51.6)
Duration of diabetes (years)	6.4 (3.7)
HbA1c, %	9.3 (1.1)
BMI z-score	0.7 (0.9)
Weight Status	
Under- or normal weight	76 (62.3)
Overweight	27 (22.1)
Obese	19 (15.6)
Insulin dose per kg, U	1.0 (0.3)
Moderate to vigorous exercise, h/day	2.7 (1.7)
Electronic media time, h/day	2.7 (2.1)
Insulin Regimen	
Multiple daily injection	32 (26.2)
Pump	90 (73.8)

Data are mean (SD) or n (%).

Abbreviations: HbA1c = Hemoglobin A1c. BMI z-score = Body Mass Index z-score.

Table 2.

Descriptive Unadjusted Analyses of Energy and Macronutrient Intake on All Days, and Days with No Hypoglycemia, Clinical Hypoglycemia, or Clinically Serious Hypoglycemia (N=122 participants; N=274 days)

	All Days (N=274)	No Hypoglycemia (n=163)	Clinical Hypoglycemia† (n=62)	Clinically Serious Hypoglycemia‡ (n=49)
Total energy, kcal	1799 (715)	1798 (685)	1804 (803)	1683 (707)
Total carbohydrates, grams	218 (97)	221 (96)	224 (101)	204 (92)
% calories from carbohydrates	48.1 (9.3)	47.8 (9.6)	48.9 (8.2)	48.1 (9.9)

Data are mean (SD).

Diet recalls were obtained from N=122 participants contributing N=274 days on which concurrent 24-hour dietary recalls and continuous glucose monitoring data were available. Participants provided between 1–4 recalls.

†Days with clinical hypoglycemia had at least one episode of hypoglycemia <70 mg/dL and ≥54 mg/dL lasting >=15 minutes. No episodes of clinically serious hypoglycemia occurred on these days. Glucose could have dropped below 54, but stayed there less than 15 minutes.

‡Days with clinically serious hypoglycemia had at least one episode of hypoglycemia <54 mg/dL lasting >=15 minutes. These days could also include episodes of clinical hypoglycemia.

Table 3.

Descriptive Unadjusted Analyses of Energy and Macronutrient Intake on Days with No Hypoglycemia, Clinical Hypoglycemia, or Clinically Serious Hypoglycemia by Day and Night (N=122 participants; N=274 days)

	Daytime Hypoglycemia (N=274)†			Nighttime Hypoglycemia (N=274)‡		
	No Hypoglycemia (n=173)	Clinical§ Hypoglycemia (n=65)	Clinically Serious ¶ Hypoglycemia (n=36)	No Hypoglycemia (n=232)	Clinical§ Hypoglycemia (n=16)	Clinically Serious¶ Hypoglycemia (n=26)
Total energy, kcal	1810 (692)	1798 (801)	1598 (658)	1786 (711)	1907 (856)	1638 (676)
Total carbohydrates (grams)	222 (98)	220 (97)	195 (88)	219 (96)	242 (118)	196 (87)
% calories from carbohydrates	47.9 (9.7)	48.7 (7.9)	48.3 (10.2)	48.1 (9.3)	49.4 (9.2)	47.7 (9.7)

Diet recalls were obtained from N=122 participants contributing N=274 days on which concurrent 24-hour dietary recalls and continuous glucose monitoring data were available. Participants provided between 1–4 recalls.

† Daytime hypoglycemia occurred between 6am–midnight. Days with no daytime hypoglycemia may have included episodes of nighttime hypoglycemia.

‡ Nighttime hypoglycemia occurred between midnight–6am. Days with no nighttime hypoglycemia may have included episodes of daytime hypoglycemia.

§ Days with clinical hypoglycemia had at least one episode of hypoglycemia <70 mg/dL and ≥54 mg/dL lasting >=15 minutes. No episodes of clinically serious hypoglycemia occurred on these days. Glucose could have dropped below 54, but stayed there less than 15 minutes.

¶ Days with clinically serious hypoglycemia had at least one episode of hypoglycemia <54 mg/dL lasting >=15 minutes. These days could also include episodes of clinical hypoglycemia.

Table 4:

Results of Unadjusted and Sequentially Adjusted Linear Mixed Models for Calorie or Carbohydrate Intake on Days with Clinical or Clinically Serious Hypoglycemia Compared to Days with No Hypoglycemia, in Youth with Type 1 Diabetes (N=122 participants; N=274 days)

	Total Calories			Carbohydrates (grams)		
	Clinical Hypoglycemia†	**Clinically Serious Hypoglycemia‡**	**Overall p-value§**	**Clinical Hypoglycemia†**	**Clinically Serious Hypoglycemia‡**	**Overall p-value§**
Model 1	22.9 (−167.5, 213.4)	−58.1 (−277.8, 161.7)	0.81	6.4 (−19.6, 32.3)	−5.8 (−36.0, 24.5)	0.77
Model 2	11.2 (−168.4, 190.7)	−66.9 (−277.9, 144.21)	0.78	6.5 (−18.3, 31.2)	−7.8 (−36.3, 20.8)	0.68
Model 3	33.0 (−135.6, 201.56)	−89 (−285.4, 107.1)	0.54	11.8 (−13.9, 37.5)	−10.0 (−38.9, 19.0)	0.42
Model 4	57.4 (−126.7, 241.5)	−74.0 (−285.9, 137.9)	0.56	12.6 (−12.7, 38.0)	−7.8 (−36.8, 21.1)	0.43

Diet recalls were obtained from N=122 participants contributing N=274 days on which concurrent 24-hour dietary recalls and continuous glucose monitoring data were available. Participants provided between 1–4 recalls.

† Days with clinical hypoglycemia had at least one episode of hypoglycemia between <70 mg/dL and ≥54 mg/dL lasting ≥15 minutes. No episodes of clinically serious hypoglycemia occurred on these days. Glucose could have dropped below 54, but stayed there less than 15 minutes. The estimate was calculated using days with no hypoglycemia as the reference group.

‡ Days with clinically serious hypoglycemia had at least one episode of hypoglycemia <54 mg/dL lasting ≥15 minutes. These days could also include episodes of clinical hypoglycemia. The estimate was calculated using days with no hypoglycemia as the reference group.

§ Overall p-values are for 3-group contrasts comparing calories or carbohydrates consumed on days with no hypoglycemia, days with clinical hypoglycemia, and days with clinically serious hypoglycemia.

Sequentially Adjusted Models:

Model 1: Unadjusted with repeated measures (Study ID, Site, and Recall [1–4])

Model 2: Random effect for Site; Group (Intervention and Control), Timepoint (baseline and follow-up)

Model 3: Demographic factors (age, sex, race/ethnicity). Nonwhite 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.

Model 4: Clinical factors (Diabetes duration, Insulin Regimen, Insulin dose, HbA1c, Physical activity, Electronic media time)

Table 5.

Results of Unadjusted and Sequentially Adjusted Linear Mixed Models for Calories and Carbohydrates Consumed on Days with Clinical or Clinically Serious Hypoglycemia Compared to Days with No Hypoglycemia, by Day- and Nighttime Hypoglycemia, in Youth with Type 1 Diabetes (N=122 participants; N=274 days)

	Calories: Daytime hypoglycemia†			Calories: Nighttime hypoglycemia‡		
	Clinical Hypoglycemia§	Clinically Serious Hypoglycemia¶	Overall p-value for 3 -group contrast	Clinical Hypoglycemia§	Clinically Serious Hypoglycemia¶	Overall p-value for 3 -group contrast
Model 1	28.8 (−155.8, 213.3)	−189.5 (−440.9, 62.0)	0.26	30.1 (−283.9, 344.0)	−87.4 (−342.6, 167.7)	0.77
Model 2	35.2 (−153.0, 223.3)	−192.1 (−446.1, 62.0)	0.25	23.7 (−284.5, 331.9)	−98.7 (−354.0, 156.6)	0.73
Model 3	25.4 (−140.6, 191.4)	−183.9 (−413.1, 45.2)	0.23	71.6 (−203.0, 346.2)	−102.4 (−329.0, 124.3)	0.56
Model 4	48.3 (−132.6, 229.1)	−166.0 (−410.1, 78.1)	0.28	96.2 (−204.2, 396.7)	−92.0 (−340.0, 155.9)	0.60
	Carbohydrates: Daytime hypoglycemia†			Carbohydrates: Nighttime hypoglycemia‡		
	Clinical Hypoglycemia§	Clinically Serious Hypoglycemia¶	Overall p-value for 3 -group contrast	Clinical Hypoglycemia§	Clinically Serious Hypoglycemia¶	Overall p-value for 3 -group contrast
Model 1	4.1 (−21.1, 29.3)	−18.0 (−52.4, 16.3)	0.49	21.5 (−22.1, 65.1)	−13.7 (−49.1, 21.8)	0.42
Model 2	4.6 (−19.1, 28.3)	−20.0 (−51.9, 11.8)	0.36	21.5 (−22.5, 65.5)	−12.6 (−48.5, 23.2)	0.45
Model 3	7.0 (−17.3, 31.3)	−18.6 (−50.7, 13.6)	0.36	28.0 (−14.0, 70.0)	−16.6 (−50.5, 17.2)	0.23
Model 4	8.8 (−16.5, 34.2)	−16.2 (−50.0, 17.5)	0.40	29.7 (−13.3, 72.7)	−14.9 (−49.8, 20.0)	0.24

Diet recalls were obtained from N=122 participants contributing N=274 days on which concurrent 24-hour dietary recalls and continuous glucose monitoring data were available. Participants provided between 1–4 recalls. Estimates were calculated using days with no hypoglycemia as the reference group. Overall p-values are for 3-group contrasts comparing calories or carbohydrates consumed on days with no hypoglycemia, days with clinical hypoglycemia, and days with clinically serious hypoglycemia.

† Daytime hypoglycemia defined as days on which hypoglycemia occurred between 6am–midnight.

‡ Nighttime hypoglycemia defined as days on which hypoglycemia occurred between midnight–6am.

§ Days with clinical hypoglycemia had at least one episode of hypoglycemia between <70 mg/dL and ≥54 mg/dL lasting ≥15 minutes. No episodes of clinically serious hypoglycemia occurred on these days. Glucose could have dropped below 54, but stayed there less than 15 minutes.

¶ Days with clinically serious hypoglycemia had at least one episode of hypoglycemia <54 mg/dL lasting ≥15 minutes. These days could also include episodes of clinical hypoglycemia.

Sequentially Adjusted Models:

Model 1: Unadjusted with repeated measures (Study ID, Site, and Recall [1–4])

Model 2: Random effect for Site; Group (Intervention and Control), Timepoint (baseline and follow-up)

Model 3: Demographic factors (age, sex, race/ethnicity). Nonwhite 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.

Model 4: Clinical factors (Diabetes duration, Insulin Regimen, Insulin dose, HbA1c, Physical activity, Electronic media time)