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Low Fat vs. High Fat Bedtime Snacks in Children and Adolescents with Type 1 Diabetes

The Diabetes Research in Children Network (DirecNet) Study Group

Abstract

Objective—The purpose of this study was to determine whether, in a group of children with Type 1 diabetes utilizing insulin pump, a pre-bedtime snack with a relatively high fat content provides greater protection from nocturnal hypoglycemia than a snack containing the same amount of carbohydrate and protein, but a lower fat content.

Research Design and Methods—Ten subjects, aged 6–<18 years, in a trial evaluating the Abbott Navigator glucose sensor, agreed to this ancillary study. On ≥ 12 separate nights, each subject was randomized via a website to a carbohydrate-low fat (30 gm CHO, 2.5 gm protein, 1.3 gm fat; 138 kCal) snack or a carbohydrate-high fat (30 gm CHO, 2 gm protein, 20 gm fat; 320 kCal) snack. Subjects used their usual evening snack algorithm to determine the size (in 15 gram carbohydrate increments) and insulin dosage.

Results—Average glucose on 128 valid study nights before snack was similar in both groups. The proportion of nights with hypoglycemia (a sensor or meter glucose value ≤ 70 mg/dL) was similar in both groups (19% high fat vs. 20% low fat) as was the proportion of nights with hyperglycemia (a glucose ≥ 200 mg/dL and at least 50mg/dL above baseline, 35% high fat vs. 30% low fat).

Conclusions—There were no statistical differences between the high and low fat snacks on the frequency of hyperglycemia or of hypoglycemia. This study highlights the feasibility of web based research in patients' home environment.

Keywords

Hypoglycemia; Glucose Sensor(s); Web-based data collections

Introduction

Children with type 1 diabetes (T1D) are particularly prone to the development of hypoglycemia, due both to marked day-to-day fluctuations in diet and physical activity and diminished ability to recognize and report hypoglycemic symptoms. In both the DCCT and prospective studies of pediatric diabetes practices (1–3), severe hypoglycemia was seen more commonly in children attempting to achieve intensive glycemic targets. Nocturnal hypoglycemia, which is frequently asymptomatic and prolonged, may lead to counter-regulatory failure and hypoglycemia unawareness, and has been demonstrated to occur in up to 50% of young children (4). Furthermore, pre-bedtime blood glucose levels may not accurately predict overnight glycemic trends, particularly following daytime exercise (5).

A common strategy long recommended by diabetes clinicians to prevent nocturnal hypoglycemia is the ingestion of a bedtime snack. The optimal composition of this snack,

however, is controversial and relatively poorly studied, especially in children and adolescents with T1D. It has been suggested that ingestion of a snack containing fat as well as carbohydrate provides longer protection against hypoglycemia than a snack containing carbohydrate alone (6). The proposed mechanisms for this effect involve fat-induced slowing of gastric emptying thereby extending the duration of carbohydrate absorption in the proximal small intestine (7).

Most previous studies that have examined the effect of bedtime snacking on the risk of nocturnal hypoglycemia have failed to take into consideration variations in daytime physical activity that predispose to nocturnal hypoglycemic events (5). Indeed, since these studies predated the introduction of continuous glucose monitoring techniques, most were performed in sedentary subjects in inpatient research center settings in order to measure plasma glucose levels frequently during the night. Moreover, the logistical and financial difficulties in carrying out such inpatient protocols generally limited the studies to testing of each snack in each subject on only a few nights in a somewhat artificial setting (8). It should also be noted that earlier studies may have limited relevance to current modalities of diabetes management, in that basal insulin replacement regimens in earlier studies were typically accomplished with NPH insulin. Reduced episodes of nocturnal hypoglycemia in children have been seen with the use of the long-acting insulin analog glargine (9,10) and with insulin pump therapy (11,12). There is little information about optimal snack composition with these newer modalities of insulin therapy.

The purpose of this study was to determine whether, in a group of children with T1D utilizing insulin pump as basal insulin replacement, a snack with carbohydrate and relatively high fat content provides greater protection from nocturnal hypoglycemia than a bedtime snack containing the same amount of carbohydrate and protein, but a lower fat content. The study utilized the FreeStyle Navigator continuous glucose monitoring device to assess the frequency of nocturnal hypoglycemia in the home setting with randomized ingestion of the two test snacks on multiple nights.

Methods

The study was conducted by the Diabetes Research in Children Network (DirecNet) at five clinical centers as an ancillary study to a study evaluating the use of the FreeStyle Navigator™ Continuous Glucose Monitoring System (“Navigator”, Abbott Diabetes Care, Alameda, CA) (13). A Data and Safety Monitoring Board and the Institutional Review Boards at each center approved the study protocol, consent form and assent form. A parent or guardian and each subject 7 years and older gave written consent and assent, respectively.

The primary eligibility requirements were: 1) age between 3 and <18 years, 2) clinical diagnosis of T1D of ≥ 1 year duration, 3) use of insulin pump for at least 6 months and 4) home computer with e-mail access. There was no pre-specified HbA1c requirement for eligibility. After completing the first 6 months of the Navigator use study, subjects were given the opportunity to participate in this study concurrently with continued use of the Navigator. The 10 subjects included in this study was a convenience sample size not based on statistical principles.

The protocol consisted of a minimum of 12 nights during which each subject consumed a low fat snack on 6 nights and a high fat snack on the other 6 nights. Protein and carbohydrate content was similar between the two snacks. A minimization algorithm was used to determine the ordering of the snack types, balancing on the pre-snack meter glucose level and self-reported amount of activity during that day (each defined as dichotomous variables). Each night prior to the bedtime snack, the subject checked his/her glucose level with the FreeStyle meter built into the Navigator. If the glucose level was < 80 mg/dL, carbohydrate (such as juice) was taken and the glucose level rechecked until the glucose level was ≥ 80 mg/dL. The last value was considered the pre-snack glucose level. On the DirecNet website, the subject entered the pre-

snack glucose level, the level of activity during that day, the amount of carbohydrates to be taken for the bedtime snack, and the amount of insulin to be taken to cover the bedtime snack. Prior to being informed as to whether to have the high-fat or low-fat snack each night, the subject used his/her usual practices for determining the amount of carbohydrate (in 15 gram increments) in the bedtime snack and amount of insulin to be given. The amount of insulin delivered each night was not verified in this study. Upon submission of the data, the website instructed the subject on which snack (high-fat or low-fat) should be eaten on that night.

The high-fat snack consisted of potato chips which for each 30 grams of carbohydrate contained 20 grams of total fat, 5 grams of saturated fat, 2 grams of protein, and 320 calories. The low fat snack consisted of pretzels which for each 30 grams of carbohydrate contained 1.3 grams of total fat, no saturated fat, 2.5 grams of protein, and 138 calories.

The Navigator was used during each of the nights of the study. After the 12 nights were completed, the Navigator data were reviewed. If there are not at least 12 nights with at least 5 hours of sensor data, data were collected for additional nights.

The primary outcome was hypoglycemia, defined as at least one glucose value ≤ 70 mg/dL on either the Navigator or the FreeStyle meter. Hyperglycemia was defined as at least one value ≥ 200 mg/dL and at least 50 mg/dL above pre-snack Navigator glucose value on either the Navigator or the FreeStyle meter.

Only nights with at least 5 hours of Navigator values between the snack and 6am were used in the analysis. This included 11 nights where pre-snack meter glucose was initially < 80 mg/dL and followed by the carbohydrate treatment. Results were similar when we excluded those 11 nights (data not shown). Glycemic indices based on the Navigator data (mean glucose over night, percentage of glucose values ≤ 70 mg/dL and percentage of glucose values ≥ 200 mg/dL) were calculated.

Hypoglycemia and hyperglycemia binary outcomes were analyzed using repeated measures regression models controlling for the pre-snack glucose level, reported activity level during that day (high, low), and the hours of glucose readings. The reported adjusted mean differences were from this model. A permutation test was used to account for the correlated data from the same subject for the comparisons of time to first hypoglycemic event and time to first hyperglycemic event.

Results

The study included 10 subjects ranging from 6 to 18 years (mean 12.4 ± 3.2 years) with diabetes for a mean of 5.9 ± 2.4 years and a mean body mass index percentile of $71\% \pm 21\%$. Seven subjects were male and 9 were Caucasian. The most recent HbA1c prior to the start of the study (measured with the DCA 2000® + Analyzer, Bayer, Inc., Tarrytown, NY) averaged $6.9 \pm 0.5\%$, with 5 being $< 7.0\%$ and 5 being $\geq 7.0\%$. In the 2 weeks prior to the start of snack study, 7 subjects were wearing Navigator sensors for at least 5 hours on 47 nights (10pm–6am), ranging from 2 to 13 nights per subject. The overnight mean glucose value on the 47 nights was 164 ± 49 mg/dL, the nocturnal hypoglycemia rate was 26%, and 3.5% of glucose values were below 70mg/dL and 29% above 200mg/dL.

The analysis included 128 nights, ranging from 12 to 15 per subject. A high-fat snack was assigned on 62 nights and a low-fat snack on 66 nights. The mean number of hours of Navigator glucose values per night was 8.0 ± 1.4 hours on high-fat nights and 8.2 ± 1.1 hours on low-fat nights. The mean pre-snack glucose level was 163 ± 55 mg/dL on the high-fat nights and 164 ± 53 mg/dL on the low-fat nights measured with the FreeStyle meter and 162 ± 60 and 165 ± 54 mg/dL, respectively, measured with the Navigator. Activity level earlier in the day was

reported as active on 12 nights in each group. The mean bedtime insulin bolus and the mean amount of carbohydrate in the snack were similar on the high-fat and low-fat nights.

Overnight, the mean glucose (measured with the Navigator) was 171 ± 46 mg/dL on high-fat nights and 156 ± 45 mg/dL on low-fat nights (adjusted mean difference = 17, 95% confidence interval 2 to 31, Figure 1); 3.1% of glucose values were ≤ 70 mg/dL on high-fat nights and 3.5% on low-fat nights (adjusted mean difference = -1.2%, 95% confidence interval -4.7% to 2.2%), while 30% and 19% of values, respectively, were ≥ 200 mg/dL (adjusted mean difference = 12%, 95% confidence interval 3% to 21%).

Hypoglycemia (at least one glucose value ≤ 70 mg/dL) occurred on 12 (19%) nights following a high-fat snack and on 13 (20%) nights following a low-fat snack (adjusted mean difference = -2%, 95% confidence interval -14% to 11%). Twenty-four of the 25 events were identified from the Navigator glucose values and one from FreeStyle values only. There was no significant difference in the time to the first hypoglycemic event between groups ($P=0.93$, Figure 2A).

Hyperglycemia (≥ 200 mg/dL and at least 50 mg/dL above pre-snack Navigator glucose) occurred on 22 (35%) nights following a high-fat snack and on 20 (30%) nights following a low fat snack (adjusted mean difference = 6%, 95% confidence interval -9% to 22%). There was no significant difference in the time to the first hyperglycemic event (as defined above) between groups ($P=0.61$, Figure 2B).

Discussion

DirecNet recently reported on the accuracy of the FreeStyle Navigator (14). Most important for this study, the Navigator was found to be as accurate during home use as it was during hospital use and during the night as it was during the day (14). The availability of this system allowed us to conduct the current study in the home environment over a large number of nights, albeit in a relatively small number of subjects. An innovative web-based system was used to select and balance the type of snack to be ingested on each of the study nights based on the pre-snack glucose level, the level of activity during that day, the amount of carbohydrates to be taken for the bedtime snack, and the amount of insulin to be taken to cover the bedtime snack.

Despite the fact that these subjects had utilized the Navigator for up to 26 weeks and that they took the usual amount of carbohydrate for their bedtime snack, nocturnal hypoglycemia (glucose ≤ 70 mg/dL) was observed during 20% of study nights, reflecting the high risk of nocturnal hypoglycemia in well-controlled patients. The most important finding of the study is that selectively increasing the amount of fat in the bedtime snack had no impact on the risk of nocturnal hypoglycemia. We failed to observe a reduction in nocturnal hypoglycemic events with the high fat snack even though glucose values tended to be slightly higher on those nights. One of the limitations of this study is that the snacks were not isocaloric. The routine addition of 182 calories per day at bedtime, overtime, could result in a possible additional gain of ~2 1/2 pounds per month unless balanced by calorie cuts at other times during the day, potentially increasing adiposity and need for more insulin. Thus the high fat snack more than doubled the amount of calories in the snack without providing any protective benefit. While it has previously been shown that a high-fat meal delays carbohydrate absorption (6), gastric emptying studies were not carried out to determine whether the differences in the amount of fat in the two snacks used in this study altered gastric emptying. However, if such an effect had occurred, it was insufficient to alter the timing or the frequency of nighttime hypoglycemia.

Since most families rely on a bedtime snack as their primary defense against nocturnal hypoglycemia, the negative results of our study are disappointing. However, the methods used

in the investigation open a way to comprehensively study the impact of other strategies to prevent nocturnal hypoglycemia, such as altering different components of the snack with the addition of cornstarch (15), protein or amino acids (16) or terbutaline (8). One outcome that we did not test in this study is whether children and adolescents with T1D could do as well or better without any bedtime snack. Like our subjects, many youth with T1D are currently overweight and eliminating the requirement of a bedtime snack could be of benefit.

In conclusion, increasing the fat content while keeping the carbohydrate content constant in the bedtime snack had no impact on the risk of nocturnal hypoglycemia while increasing total daily calories. There was no reduction in nocturnal hypoglycemic events with the high fat snack, although the glucose values tended to be slightly higher on those nights. Further studies of bedtime snack composition are necessary to determine more effective ways to reduce the risk of nocturnal hypoglycemia in children with diabetes.

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Appendix

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Figure 1. Mean Sensor glucose at Each Hour after Bedtime Snack

Pre-snack Navigator glucose was defined as mean sensor glucose over 30 minutes prior to snack. Glucose at each hour after snack was the average of 3 sensor glucose readings (half-hour data) around the time. The error bars represent the pointwise 95% confidence interval.

Figure 2. Hypoglycemia and Hyperglycemia for the High-fat and Low-fat Nights
 (A). Time to and frequency of hypoglycemia for the high-fat and low-fat nights.
 (B). Time to and frequency of hyperglycemia for the high-fat and low-fat nights.