Journal of Diabetes and Its Complications xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Dietary intake and risk of non-severe hypoglycemia in adolescents with type 1 diabetes

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ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 29 March 2017
Accepted 16 April 2017
Available online xxxx

Keywords:
Type 1 diabetes
Dietary intake
Nutrition
Hypoglycemia
Continuous glucose monitoring

ABSTRACT

Aims: To determine the association between dietary intake and risk of non-severe hypoglycemia in adolescents with type 1 diabetes.
Methods: Type 1 adolescents from a randomized trial wore a blinded continuous glucose monitoring (CGM) system at baseline for one week in free-living conditions. Dietary intake was calculated as the average from two 24-h dietary recalls. Non-severe hypoglycemia was defined as having blood glucose <70 mg/dL for ≥10 min but not requiring external assistance, categorized as daytime and nocturnal (11 PM–7AM). Data were analyzed using logistic regression models.
Results: Among 98 participants with 14,277 h of CGM data, 70 had daytime hypoglycemia, 66 had nocturnal hypoglycemia, 55 had both, and 17 had neither. Soluble fiber and protein intake were positively associated with both daytime and nocturnal hypoglycemia. Glycemic index, monounsaturated fat, and polyunsaturated fat were negatively associated with daytime hypoglycemia only. Adjusting for total daily insulin dose per kilogram eliminated all associations.
Conclusions: Dietary intake was differentially associated with daytime and nocturnal hypoglycemia. Over 80% of type 1 adolescents had hypoglycemia in a week, which may be attributed to the mismatch between optimal insulin dose needed for each meal and actually delivered insulin dose without considering quality of carbohydrate and nutrients beyond carbohydrate.
Clinical trial registration: ClinicalTrials.gov identifier: NCT01286350.

1. Introduction

Hypoglycemia occurs frequently in people with type 1 diabetes with an incidence of over 1–2 episodes per week per patient.[1] Youth with type 1 diabetes are particularly vulnerable to hypoglycemia due to unpredictable food consumption, erratic physical activity, and problems with accurate insulin dosing and detecting hypoglycemia.[2,3] Further, their brains are still developing, which put them at risk of cognitive dysfunction and neurological sequelae of hyperglycemia[4] and hypoglycemia.[5,6]

Hypoglycemia is preventable and nutrition therapy plays a pivotal role in this.[7] Current nutrition guidelines are very specific about how to treat hypoglycemia when it occurs.[2] However, information regarding

Funding: This study was supported by NIH/NIDDK (1UC4DK101132) and Helmsley Charitable Trust.

Declaration of interest: VWZ is funded by the Sanofi Global Nutrition Scholars program at the University of North Carolina at Chapel Hill. CMS is an employee of the American Heart Association. JJ is an employee of Sanofi US. DMM is on the advisory board for Insulet, consults for Abbott Diabetes Care, and his non-profit employer has received research funding from Medtronic, Dexcom, and Roche. All other authors declare no conflict of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2017.04.017
1056-8727/

whether or how usual dietary intake influences risk of hypoglycemia is limited, particularly for children with diabetes. Medical nutrition therapy designed for adults may not be applicable to children, and it may even conflict with the evidence rising from pediatric populations.[7,8] Further, the literature has primarily focused on postprandial glycemic excursions following experimental meals in clinical trial settings, which are directly related to acute dietary effect on blood glucose after consuming test meals.[8–10] Yet, no study has examined the effect of usual dietary intake on risk of hypoglycemia measured by continuous glucose monitor (CGM) in free-living youth with type 1 diabetes, which associates typical dietary patterns with day-to-day glycemic control.

Non-severe hypoglycemia accounts for 88–98% of all hypoglycemic events in patients with diabetes,[11] which is defined as a low blood glucose event <70 mg/dL but does not require external assistance.[5] Complete quantification of non-severe hypoglycemia in an outpatient setting typically requires CGM. CGM-defined hypoglycemia is recommended by a consensus statement from the American Diabetes Association as an outcome measure, in addition to HbA1c, for evaluating glucose control in people with type 1 diabetes.[12] In this study, we aimed to determine the association between usual dietary intake and risk of developing non-severe hypoglycemia in a sample of adolescents with type 1 diabetes who wore CGM in a one-week period at baseline from the Flexible Lifestyle Empowering Change (FL3X) randomized clinical trial (ClinicalTrials.gov identifier: NCT01286350).

2. Participants and methods

2.1. Participants

The FL3X is an 18-month randomized trial with the primary goal of improving glycemic control and quality of life in adolescents with type 1 diabetes through an evidence-based flexible lifestyle intervention. The intervention focuses on increasing adherence to type 1 diabetes self-management including medical therapy, diet, and physical activity. Eligible participants were aged 13–16 years at study entry and had HbA1c 8–13% and duration of diabetes >1 year. Participants were enrolled from two sites: 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. Written informed consent was obtained from parents or legal guardians. The current study used baseline data from a subset of 258 adolescents with type 1 diabetes from the FL3X trial who also participated in the ancillary study: *Measures of Hypoglycemia and Glycemic Variability Using Continuous Glucose Monitoring*. The ancillary study was funded separately from the FL3X trial. Of all 258 participants, 95 had completed baseline data collection when the funding was received, and thus were excluded for the ancillary study. Additional 33 participants were excluded due to participation refusal (n = 4), not-completed data collection (n =13), no dietary recall conducted (n = 12), and other reasons (n = 4). Accordingly, 130 participants who had at least one completed dietary recall comprised our final study sample. The study protocol was approved by the Institutional Review Boards at each participating site. The study was conducted in accordance with the Declaration of Helsinki. For this investigation, data were collected during one week period of time at baseline.

2.2. Measuring blood glucose using CGM

At the baseline visit, the iPro2 CGM system (Medtronic Inc.) with the Enlite sensor was inserted into the abdominal subcutaneous adipose tissue. Participants were carefully instructed on the use and maintenance of the CGM system and were advised to calibrate the sensor before eating and before bed with iPro2 compatible glucometer (OneTouch Ultra2). The Enlite sensor measured interstitial glucose level every five min within a range 40–400 mg/dL. On the last day of the CGM wearing week, participants were reminded to send the device back, using the pre-paid box/envelope given at the end of the study visit in the first day. The CGM data were downloaded with CareLink iPro System and uploaded to the coordinating center for data processing. CGM readings were blinded to participants. No alarms for hypoglycemia or hyperglycemia or any communication from the device were available to participants.

2.3. 24-h dietary and physical activity recalls

Telephone-administered 24-h dietary recalls were administered to participants (ideally one weekday and one weekend day) to ascertain dietary intake. Interviews were conducted by trained and certified interviewers from the UNC NIH/NIDDK Nutrition Obesity Research Center (NORC) staff (P30DK056350; MPI Mayer-Davis), using the Nutrient Data System for Research software (NDSR Version 2014, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) and the multiple pass interviewing method.[13,14]

The validated Previous Day Physical Activity Recall (PDPAR)[15,16] divided the day into half-hour time blocks and queried the dominant activity and the approximate intensity of that activity for each period. The intensity level was categorized as light (slow breathing, little or no movement), moderate (normal breathing and some movement), hard (increased breathing and moderate movement), and vary hard (hard breathing and quick movement).The PDPAR was under the direction of the UNC NORC and administered concurrently with the 24-h dietary recalls.

2.4. Other data

Standardized questionnaires were used to collect self-reported data including race, highest level of parental education, duration of diabetes, insulin delivery method, and insulin dose. Weight, height, and HbA1c level were measured or assayed according to standardized protocols.

Body mass index (BMI) was computed and converted to a BMI z score using the Center for Disease Control/National Center for Health Statistics 2000 reference curves.[17]

2.5. Statistical analysis

No severe hypoglycemic events were reported during the study week. Non-severe hypoglycemic events were defined as having CGM reading <70 mg/dL for 10 min or more.[18,19] They were further categorized into daytime and nocturnal non-severe hypoglycemia. This distinction is important because current insulin analogues and subcutaneous delivery methods do not adequately mimic normal physiologic patterns of insulin secretion[20] and sleep attenuates counter-regulatory responses to hypoglycemia.[21] Further, dietary intake and exercise[22] as two major determinants of blood glucose occur mainly in the daytime. Accordingly, dietary intake is likely to influence hypoglycemia risk differently during the day and night. Hypoglycemia that occurred between 11:00 PM and 7:00 AM was defined as nocturnal hypoglycemia.[18,23]

Usual daily dietary intake in the study week was averaged from two 24-h dietary recalls. Macronutrients of interest were total carbohydrate, total protein, animal protein, plant protein, total fat, saturated fat (SFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA), ratio of MUFA to SFA (MUFA/SFA), and ratio of PUFA to SFA (PUFA/SFA). Total fiber, soluble fiber (e.g., fiber in oat bran, barley, seeds, nuts, and lentils), insoluble fiber, glycemic index (GI), and glycemic load (GL) were also studied.

Patients with no dietary recall, one recall only, and two recalls were compared. Further, for those with two dietary recalls, patient characteristics and average daily dietary intake were compared among four groups of participants: no hypoglycemia, daytime hypoglycemia only, nocturnal hypoglycemia only, and both daytime

Please cite this article as: Zhong VW, et al. Dietary intake and risk of non-severe hypoglycemia in adolescents with type 1 diabetes. *Journal of Diabetes and Its Complications* (2017), http://dx.doi.org/10.1016/j.jdiacomp.2017.04.017