HHS Public Access

Author manuscript

J Diabetes Complications. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

J Diabetes Complications. 2017 April ; 31(4): 735–741. doi:10.1016/j.jdiacomp.2016.12.015.

Fear of Hypoglycemia: Influence on Glycemic Variability and Self-Management Behavior in Young Adults with Type 1 Diabetes

Pamela Martyn-Nemeth[a], **Laurie Quinn**[a], **Sue Penckofer**[b], **Chang Park**[a], **Vanessa Hofer**[c], and **Larisa Burke**[a]

[a]University of Illinois at Chicago, College of Nursing, Chicago, IL

[b]Loyola University Chicago, Marcella Niehoff School of Nursing, Chicago, IL

[c]Rush University, College of Nursing, Chicago, IL

Abstract

Purpose—The purpose of this study was to examine how fear of hypoglycemia (FOH) is associated with glycemic variability (GV) and self-management behavior in young adults (aged 18–35) with type 1 diabetes (T1DM).

Procedures—Using a prospective repeated-measures design, in 35 young adults, within- and between-person and temporal associations of FOH, specific self-management behaviors, and GV were measured. The data were collected using questionnaires and real-time measures using daily diaries, insulin pump downloads, actigraphy, and continuous glucose monitoring.

Findings—FOH was associated with greater glycemic variability. Significant temporal associations emerged. Concurrent day (glucose SD, $p = .011$) and previous-evening fear levels were associated with GV (glucose SD, $p = .007$). FOH was also associated with greater calorie intake ($r = .492$, $p = .003$) and less physical activity (light activity, $r = -.341$, $p = .045$).

Conclusions—The significant associations of FOH with GV, dietary patterns, and physical activity provide evidence for FOH as an important psychological factor associated with diabetes care.

Keywords

Fear of hypoglycemia; type 1 diabetes; glycemic variability; self-management; behavior

1. Introduction

Near-normal glucose levels can reduce the occurrence and progression of diabetes-related complications (Diabetes Control and Complications Trial (DCCT) Research Group, 1994).

Corresponding Author: Pamela Martyn-Nemeth, PhD, RN, Assistant Professor, University of Illinois at Chicago College of Nursing, Department of Biobehavioral Health Science, 845 South Damen Avenue (MC 802), Chicago, IL 60612, (312) 996 7903 (Phone), pmartyn@uic.edu.

However, as blood glucose approaches near-normal levels, the risk increases for hypoglycemia. Hypoglycemia is life-threatening and can lead to serious physical and psychological sequelae and can in turn lead to profound fear of future hypoglycemic episodes (Vallis, Jones, & Pouwer, 2014). These distressing negative experiences influence health behaviors used in diabetes self-management (Lawton et al., 2013). Vigilance to avoid hypoglycemia is necessary; however, fear of hypoglycemia (FOH) can lead to perceived concerns of a mismatch between food intake (Richmond, 1996; Wu, Juang, & Yeh, 2011), insulin dose (Richmond, 1996), or physical activity (Brazeau et al., 2012), resulting in over- or under-compensatory behaviors.

1.1. Why is Glycemic Variability Important?

As a result of the over- or under-compensatory behaviors in response to FOH, blood glucose levels can vary greatly, leading to increased glycemic variability (GV; Gonder-Frederick et al., 2013). GV is defined as the intraday fluctuation in blood glucose (Cameron, Donath, & Baghurst, 2010). Emerging evidence supports the role that GV plays in the generation of oxidative stress (Quagliaro et al., 2003), endothelial dysfunction (Ceriello et al., 2012), and diabetes complications (Soupal et al., 2014). High degrees of GV are associated with more frequent episodes of hypoglycemia (Kilpatrick, Rigby, Goode, & Atkin, 2007) and glucose extremes (i.e., hypo- to hyperglycemic levels), which may occur with overtreatment of a hypoglycemic episode. GV is influenced by self-management behavior (Kildegaard, Christensen, & Hejlesen, 2009) and is amenable to change with appropriate intervention. The use of continuous glucose monitoring (CGM) allows measurement of 24-hour GV to better explore this problem. To our knowledge, the relationship of FOH to GV has not been examined using CGM technology. Young adults may be at particular risk for GV because they report higher FOH levels than adolescents (Bohme, Bertin, Cosson, & Chevalier, 2013); thus, it is critical to develop strategies to assist young adults in coping with FOH.

1.2. What Self-Management Behaviors may be Associated with FOH?

Changing dietary intake is a frequent strategy used in response to FOH (Richmond, 1996). Dietary modifications may include excessive eating (Ahola, 2016; Richmond, 1996), overcorrecting a hypoglycemic episode (Savard et al., 2016), or snacking at night (Desjardins, Brazeau, Strychar, & Rabasa-Lhoret, 2014; Weiner & Skipper, 1978). Stress-induced eating has been linked to diabetes distress (Martyn-Nemeth, Quinn, Hacker, Park, & Kujath, 2014), and binging in response to hypoglycemia is commonly reported (Lawton et al., 2013). In terms of medication management, insulin doses may be inappropriately reduced in anticipation or fear of future hypoglycemia (Di Battista, Hart, Greco, & Gloizer, 2009).

FOH has been reported to be a major barrier to engaging in a regular physical activity/exercise program (Brazeau, Rabasa-Lhoret, Strychar, & Mircescu, 2008; Pinsker et al., 2016). Certain types of activity may be limited due to the perception of a greater risk of hypoglycemia and difficulty managing it (Lascar et al., 2014). Many struggle to adhere to the recommended guidelines due to anxiety, FOH, and habituated responses to FOH (Lawton et al., 2013).

The purpose of this study was to examine how FOH is associated with GV and self-management behavior in young adults (aged 18–35) with T1DM. Young adults are an important group to study because they have reported high FOH levels (Bohme et al., 2013) and are in a critical developmental stage when they are entering the workforce, planning their families, and becoming financially independent (Arnett, 2001), all within the context of managing a chronic illness.

The specific aims were to examine: (1) the association of FOH with GV and (2) associations of FOH with self-management behaviors (dietary patterns, carbohydrate intake, insulin dosing, and physical activity); and to examine temporal associations of each.

2. Material and Methods

A prospective repeated-measures design was used with real-time event monitoring, questionnaires, and a daily fear diary. The data were collected over six consecutive days.

2.1. Setting/Sample

English-speaking men and women, aged 18 to 35 years, diagnosed with T1DM for at least one year, and using an insulin pump, were eligible to participate in the study. Subjects were excluded if pregnant; had cognitive or physical disorders that would impair the ability to use CGM and actigraphy monitors; or had a recent hospitalization (past month) for metabolic decompensation. Thirty-seven subjects were recruited using patient letters, flyers, and e-announcements at the University of Illinois at Chicago (UIC), as well as e-postings and flyers on local diabetes websites and distributed at local diabetes health fairs and events.

2.2. Variables and Measures

2.2.1. Fear of hypoglycemia—(FOH) was measured using in two ways (for baseline trait FOH and daily FOH; Table 1). *Baseline trait FOH* was measured with the worry subscale of the Hypoglycemia Fear Scale II (HFSII; Gonder-Frederick et al., 2011) at the initial visit. This is an 18-item, 5-point (*never* to *very often*), Likert-style scale that measures the frequency of situation-specific worries about hypoglycemia. Higher scores indicate greater FOH. The subscale has strong psychometric properties (Cronbach's alpha 0.95; convergent and construct validity demonstrated [Gonder-Frederick et al., 2011]).

Daily FOH was measured with a daily diary. The subjects were instructed to record their level of FOH every morning and evening using a 5-point numerical scale with anchors 1 = *not at all worried,* to 5 = *very worried.* The morning question was, "Considering your schedule today, how worried are you that you may become hypoglycemic?" The evening was, "How worried are you that you might become hypoglycemic overnight?" The diary was developed with input from T1DM individuals who experience FOH and was pilot tested on the first five subjects.

2.2.2. Glycemic Measures—Hypoglycemia measures included baseline history of hypoglycemia, daily episodes of hypoglycemia reported in the diary, and CGM-derived hypoglycemia. *Baseline history of hypoglycemia* was measured with the Hypoglycemia Patient Questionnaire (Seaquist et al., 2013). This scale is comprised of Likert-style and fill-

in responses that measure the frequency of previous hypoglycemic episodes, as well as symptoms associated with hypoglycemia and hypoglycemic awareness. This was completed at the initial visit.

Daily hypoglycemic episodes experienced during the data collection period were reported in the daily diary. At the end of each study day, the subjects recorded the number of hypoglycemic episodes, the time each occurred, the associated capillary blood glucose reading, the possible cause, and how they responded. The diary contained free space for open-ended comments.

The *CGM-derived hypoglycemic episodes* were obtained daily from the sensor by the research team. Time spent in hypoglycemia (hours and %; at < 70 mg/dl) was calculated from the CGM recordings.

Glycemic variability: Subcutaneous interstitial glucose levels were measured over six days using a CGMS® iPro2® blinded continuous glucose recorder (Medtronic, Northridge, CA). All data were downloaded to CGM Medtronic Software and examined for glycemic trends and excursions. The average interstitial glucose was recorded at five-minute intervals, resulting in 288 readings per day.

Two methods were used to examine daily GV: (1) the 24-hour standard deviation (GlucSD) derived from the 288 sensor readings and (2) the continuous overall net glycemic action (CONGA). CONGA is the calculation of within-day glucose variation for a defined period of time. The SD of the glucose between the two time points (e.g., four hours) was calculated for each observation over the 24-hour period. The mean and SD of these differences were calculated, and the SD represents the CONGA value (McDonnell, Donath, Vidmar, Werther, & Cameron, 2005). Higher CONGA values indicate greater GV. For this study, we calculated CONGA for 3-, 4-, and 6-hour intervals to reflect variability in time periods associated with diabetes management such as meals, insulin dosing, and activity (McDonnell et al., 2005).

Glycemic Control: Hemoglobin A1C was measured at baseline as an index of overall glycemic control. This was done using A1CNow® (Polymer Technology Systems, Inc., Indianapolis, IN).

2.2.3. Self-Management Behaviors—Diet, medication, and physical activity were assessed to evaluate self-management behaviors. Two methods were used to measure *dietary self-management*. (1) Dietary intake over the past 12 months was obtained using a validated food frequency questionnaire (Block 2005®) at baseline. This self-report questionnaire provides the frequency (*never* to *every day*) and portion size (using pictures) of a broad range of foods and dietary patterns. Usual nutrient intakes of carbohydrate (CHO), proteins, fats, and specific food groups were calculated using a computer software program (NutriQuest©). (2) Daily CHO intake was downloaded from the insulin pump as each subject was instructed to insert their carbohydrate (CHO grams) for all meals and snacks into their insulin pump for each of the six days. This provided a record of CHO intake in real-time that was date- and time-recorded. For this analysis, total daily CHO intake (g) was

used. To assess for *medication self-management*, total daily insulin dose, basal and bolus doses, were downloaded or transcribed from each subject's insulin pump. All insulin doses delivered by pump were date- and time-recorded. For this analysis, total daily insulin dose was used.

To assess for *physical activity self-management,* an actigraphy monitor was worn (BodyMedia SenseWear System®) on the upper arm. This validated SenseWear System® (Brazeau et al., 2016) recorded continuous physiological activity data using heat flux, galvanic skin response, skin temperature, and a three-axis accelerometer that was recorded at one-minute intervals. Daily times spent in sedentary, light, moderate, and vigorous activity were used for this analysis.

2.4. Procedures

Qualified participants were scheduled for a visit to the UIC College of Nursing. At that study visit, informed consent, pregnancy test (females), and A1C were obtained, and baseline questionnaires were administered. A CGM and an actigraphy monitor were placed, a diary was provided, and the participants were instructed on their use. The research staff followed up with a daily telephone call to answer any questions and assure consistency of data collection over the study period. On Day 3, the participants returned to the CON, or a home visit was scheduled to have the CGM site changed and insulin pump data downloaded. On Day 6, the participants returned to the CON. The remaining pump data were downloaded, and CGM and actigraphy monitors were removed. Diary recordings were collected; the participants were compensated for their time and received copies of their CGM and activity recordings.

2.5. Human Subjects

The study protocol was approved by the University of Illinois at Chicago Human Subjects Institutional Review Board. All subjects provided informed consent prior to study participation.

2.6. Data Analysis

Demographic, self-report questionnaires, and real-time repeated measures data were summarized using descriptive statistics (SPSS 24). Means were calculated for normally distributed variables and medians for those not normally distributed.

The individual subject CGM recordings were examined in detail (Figure 1). CGM recordings of 12 hours or more per day were retained for analysis. Most subjects (71%) had 20–24 hours per day of complete CGM recordings, yielding 171 usable recordings to calculate GV.

Pearson correlation coefficients were computed among FOH, GV, and self-management behaviors. No adjustment for multiple comparisons was done due to the exploratory nature of the study.

Within- and between-person associations of daily FOH, GV, and self-management behaviors (CHO intake, daily insulin dose, and daily physical activity) were analyzed at the daily level.

Known covariates were controlled: gender, age, diabetes duration, hypoglycemic episodes, and A1C. Lagged variables were created for diary-recorded daily FOH to examine the temporal associations of FOH with GV and self-management behaviors. This allowed examination of previous day (and evening) FOH with next-day GV and self-management behavior. We also examined other plausible temporal relationships (e.g. previous day GV and hypoglycemia with next-day FOH).

Lastly, a linear mixed-effects model was fitted to identify overall predictors of glycemic variability, using daily measures of FOH, GV, and self-management behaviors, controlling for gender, age, diabetes duration, hypoglycemic events, and A1C.

3. Results

Two subjects experienced CGM recording failure and were not included in the analysis. The characteristics of the final sample are delineated in Table 1. There were 35 young adults (female 63%), aged 18 to 35 years (M = 26 ± 4), diagnosed with T1DM for 1 to 31 years (13 ± 8.1). The racial/ethnic distribution was White (88%), Black (9%), multiracial (3%), and Latino (6%). Sixty percent were single; 20% married, 17% living with a partner; and 89% lived away from their parents. Most had earned a college degree or higher (86%) and were working full time (60%).

3.1. Fear of Hypoglycemia

The mean *baseline trait FOH*, measured with the HFS worry scale, was 26.6 ± 12.4. The highest worry rankings among respondents were: becoming hypoglycemic while sleeping (51%), low blood glucose interfering with important things (49%), embarrassing self in social situations (34%), and not having food available (34%).

Daily diary-recorded FOH levels spanned the full range of possible scores (from 1 = *not worried at all* to 5 = *very worried);* median value 2.0, IQR 1–3.5 (Table 1). Overall, 77% reported high daily fear levels (ranked 4 or 5) at least once during the six-day study period. Slightly more than half of participants (52%) reported greater fear in the morning, whereas 45% reported greater fear in the evening. Comments entered on the logs included: “I am never ‘not worried,’ it (FOH) is always in the background”; “I am always at least a '2' and it goes up from there.”; “I don’t know when, but I know it will happen”; “It is a chronic fear, I live with it constantly, it is never gone”; “Stress, combined with a busy day could lead to either a high or a low”; “I always worry, I won’t wake up”; and “I have no control over it.”

Trait FOH was significantly associated with daily FOH (day worry, $r = .569$, $p < .001$; evening worry $r = .505$, $p = .001$). The variability in daily FOH was examined to determine if there was an association with trait FOH. There was no significant association between these variables.

3.2. Glycemic Measures

3.2.1 Hypoglycemia—All but two subjects reported that they were able to identify their symptoms of hypoglycemia. There was no difference in hypoglycemia frequency between those who were hypo-unaware vs. those who were aware. The median frequency of

hypoglycemic episodes (< 70 mg/dl) over the past year was reported as three times per week, based on the Hypoglycemia Patient Questionnaire. Diary-recorded hypoglycemic events during the data collection period were more frequent, occurring 0–4 times per day (median 1.0). CGM-derived hypoglycemia was consistent with diary-recorded events, occurring a median of 1 hour per day (0–9.8 hours; Table 1). Diary-recorded hypoglycemic events were significantly associated with evening FOH ($p = .018$).

3.2.2 Glycemic Control and Glycemic Variability—Glycemic control and variability indices are reported in Table 1. A1C levels measured at the beginning of the study were significantly associated with GV (GlucSD, $r = .452$, $p = .006$). Despite this finding, several individuals with optimal A1C levels (i.e., 6.1%) had high GV (Figure 1). Thus, higher A1C was not consistently associated with greater GV in all subjects and did not provide a complete picture of glycemic control. A1C levels were not associated with any of the FOH measures (daily morning or evening, or trait FOH).

3.3. Self-Management Behaviors

Usual dietary intake consisted of 43% CHO, 16% protein, and 39% fat (Table 1). Daily CHO intake obtained from insulin pump downloads ranged from 20 to 490 grams per day. This included one subject who attempted to completely refrain from eating CHO to reduce insulin needs and others who ingested high CHO loads (e.g., in conjunction with drinking alcohol and eating snacks to avoid hypoglycemia). The total daily insulin doses ranged from 0.2–1.5 units/kg per day (median 0.6 units/kg/day).

Actigraphy recordings of physical activity revealed that most participants were sedentary (< 1.5 metabolic equivalents [METS]), with a median time of 16.9 hours per day. Physically active participants spent more time in light activity than moderate or vigorous activity (Table 1). Total time spent in physical activity was significantly related to A1C ($r = .362$, $p = .039$).

3.4. Aim 1. Relationship of FOH to GV

A mixed-effects model was used to examine the within- and between-subject variation of daily (morning and evening) FOH with GV (GlucSD). Significant fixed effects were observed with concurrent (same day) morning worry and glycemic variability (Table 2). Using lagged variables for FOH, temporal associations were examined between previous-day (morning and evening) FOH and next-day GV. Previous-evening FOH was significantly associated with next-day GV (Table 2). Longer time periods were not significant. Thus, both concurrent and previous-day FOH levels were associated with GV, but the temporal association did not extend beyond the previous evening. Examination showed that other plausible temporal relationships were not significant: i.e. previous-day (or evening) GV and previous-day (or evening) hypoglycemic episodes were not associated with next-day FOH (data not shown).

Aim 2. Association of FOH with Self-Management Behavior—To determine the association of FOH to *usual* dietary intake, Pearson correlation coefficients were calculated for the HFS worry subscale score (*baseline trait FOH*) and total calorie, CHO, protein, and fat intake obtained from the FFQ. Higher trait FOH was associated with greater total daily

calorie (r = .492, p = .003), CHO (r = .424, p = .012), protein (r = .461, p = .006), and fat intake (r = .507, p = .002) and significantly more servings from the grain food group (r = .425, p = .012). Greater trait FOH was also associated with less time spent in physical activity (light activity, r = −.341, p = .045).

To determine if *daily FOH* was associated with daily CHO intake, total daily insulin dose, and daily physical activity, a mixed-effects model was used to examine within- and between-person relationships. There were no significant associations between FOH and these self-management behaviors at the daily level. To determine temporal associations, lagged variables for FOH were examined between previous day FOH (morning and evening) and next-day CHO intake, total insulin dose, and physical activity (Table 2). There were no significant temporal associations present.

3.5 Overall Model for GV

Using a mixed model for fixed and random effects, the best overall model fit for factors influencing GV was sought. Overall GV was predicted by morning FOH and daily CHO intake (controlling for age, gender, diabetes duration, hypoglycemic events, and A1C; Table 3).

4. Discussion

To the best of our knowledge, this is the first study to examine FOH, GV, and self-management behavior prospectively using self-report and real-time measures. The major findings were: (1) FOH was associated with greater glycemic variability and (2) FOH was associated with higher calorie intake and less physical activity. Significant temporal relationships emerged in which concurrent-day and previous-evening FOH levels were associated with GV. These findings suggest that daily FOH serves as a psychological stressor that influences short-term GV.

Despite state-of-the-science diabetes treatment regimens with insulin pump therapy, all of the participants reported having some degree of FOH. These fear levels varied based on the context of each day. Of note, 78% reported a high FOH rating at least once during the six-day data collection period. We acknowledge that some degree of worry about hypoglycemia is appropriately adaptive and serves as a protective mechanism to prevent life-threatening hypoglycemia. High FOH levels, however, may lead to increased anxiety and result in a delay to action or inappropriate action (Adolphs, 2013; Green, Feher, & Catalan, 2000).

Consistent with previous research (Anderbro et al., 2015; Bohme et al., 2013), hypoglycemic episodes were associated with FOH. Responses on the HFS scale revealed greatest worry related to nocturnal hypoglycemia, interference of hypoglycemia with important activities, and social embarrassment. The entries on the daily diary added a broader picture of an always-present chronic fear, a feeling of inevitability of hypoglycemia and lack of control. What our study adds is that participants were asked to consider how worried they were in real-time, looking *ahead* to the schedule of the day or overnight period. To answer this question, they had to rely on their experiences and learning history to project into the future. Studies have shown that fear develops from previous negative experiences

that create a conditioned response to future fear triggers (Green et al., 2000; Hartley & Phelps, 2010). Occurrence of a similar situation may lead to anxiety. Low levels of anxiety may be motivating and stimulate an appropriate response, whereas heightened anxiety may impair awareness of internal and external blood glucose cues and leave individuals less prepared to take action (Green et al., 2000). Diabetes education programs typically address FOH but have not developed strategies to manage it (Lawton et al., 2013).

A1C was not associated with FOH in the current study, which argues against the practice of maintaining glucose consistently higher to avoid hypoglycemia in this sample. It is possible that greater GV with equivalent peaks and nadirs results in a normal A1C for some individuals. A1C has been inconsistently associated with FOH in previous research (Hanna, Weaver, Stump, Fortenberry, & DiMeglio, 2014; Hendrieckx et al., 2014; Nixon & Pickup, 2011), suggesting that short-term measures of glycemia may better depict this phenomenon.

With regard to self-management behavior, the association of trait FOH with greater calorie and macronutrient consumption supports previous reports of eating and snacking when worried (Bohme et al., 2013; Weiner & Skipper, 1978). However, daily diary fear was not related to CHO intake and insulin dosing. This may have been in part due to the fact that we calculated CHO and insulin doses as daily totals. This daily level of analysis may not have been sensitive to the shorter-term dietary and dose adjustments that occur (sometimes minute-to-minute or hour-to-hour) in response to FOH. In addition, some self-management responses to FOH may be non-linear. In our previous research, we noted a U-shaped pattern with fewer behaviors instituted at higher stress levels (Martyn-Nemeth et al., 2014). Exploration of possible nonlinear relationships in future research is warranted.

Actigraphy recordings of physical activity revealed more activity time spent in light compared to moderate or vigorous activity. Higher baseline trait FOH was related to less time spent in physical activity. These findings corroborate previous studies that identified FOH as a major barrier to physical activity (Brazeau et al., 2008; Riaz, Basit, Fawwad, Yakoob Ahmedani, & Ali Rizvi, 2014). Individuals with T1DM may be challenged to participate in regular physical activity to maintain a healthy lifestyle, yet have difficulty managing their blood glucose levels during and after the exercise bout. Physical activity can precipitate greater GV and hypoglycemia episodes (Briscoe, Tate, & Davis, 2007; Hill et al., 2016). Those who spent more time engaging in physical activity had higher A1C levels, which might reflect compensatory behaviors to avoid hypoglycemia with exercise. This finding must be interpreted with caution because of the small sample. Previous studies have found that regular physical activity and exercise was associated with improved A1C levels in adults; however, few have used randomized controlled trials, and many measures of physical activity have been self-reported (Bohn et al., 2015; Yardley, Hay, Abou-Setta, Marks, & McGavock, 2014). Additionally, the potential mediating effect of FOH on physical activity and strategies to address this problem have not been fully addressed.

4.1. Limitations

The twice-daily measures of FOH may not have been frequent enough to pair with self-management decisions. In terms of self-management measures, CHO intake was based on CHO counting accuracy, as well as adherence to entering CHO grams into the insulin pump

each time; thus, CHO intake may have been inaccurately reported. This was a convenience sample of well-educated young adults who used insulin pump therapy and had fairly good glucose control. Thus, the sample may not be representative of others with T1DM. Due to the exploratory nature of this study, a power analysis for sample size was not done. However, a post-hoc power analysis using a Monte Carlo simulation model (Landau & Stahl, 2013) based on the estimated fixed effect coefficients revealed that 35 subjects resulted in power of 0.98 for daily FOH to detect a change in GV.

5. Conclusions

In summary, prospective examination of FOH in real time revealed that FOH was temporally associated with GV. FOH was also associated with higher calorie intake and less physical activity. Our findings should be interpreted with caution due to the small sample and exploratory nature of the study. However, we raise important questions regarding the association of FOH with GV and the need to examine these factors further to develop interventions to reduce or manage FOH to promote healthy diabetes outcomes.

Acknowledgments

Supported by Chicago Center for Diabetes Translation Research (NIDDK P30 DK092949); the Dean's Office of the Biological Sciences Division of the University of Chicago; and the American Nurses Foundation. Author Disclosure Statement: No disclosures.

References

Adolphs R. The biology of fear. Curr Biol. 2013; 23(2):R79–93. DOI: 10.1016/j.cub.2012.11.055 [PubMed: 23347946]

Ahola AJ, Saraheimo M, Freese R, Makimattila S, Forsblom C, Groop PH. Fear of Hypoglycemia and self-management behavior. Journal of Clinical & Translational Endocrinology. 2016; 4:13–8.

Anderbro T, Gonder-Frederick L, Bolinder J, Lins PE, Wredling R, Moberg E, … Johansson UB. Fear of hypoglycemia: relationship to hypoglycemic risk and psychological factors. Acta Diabetol. 2015; 52(3):581–589. DOI: 10.1007/s00592-014-0694-8 [PubMed: 25528005]

Arnett J. Conceptions of the transition to adulthood: perspectives from adolescence through midlife. Journal of Adult Development. 2001; 8(2):133–143.

Bohme P, Bertin E, Cosson E, Chevalier N. Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? Diabetes & Metabolism. 2013; 39:63–70. [PubMed: 23266467]

Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, … Holl RW. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. Diabetes Care. 2015; 38(8): 1536–1543. DOI: 10.2337/dc15-0030 [PubMed: 26015557]

Brazeau AS, Beaudoin N, Belisle V, Messier V, Karelis AD, Rabasa-Lhoret R. Validation and reliability of two activity monitors for energy expenditure assessment. J Sci Med Sport. 2016; 19(1): 46–50. DOI: 10.1016/j.jsams.2014.11.001 [PubMed: 25466490]

Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008; 31(11):2108–2109. DOI: 10.2337/dc08-0720 [PubMed: 18689694]

Briscoe VJ, Tate DB, Davis SN. Type 1 diabetes: exercise and hypoglycemia. Appl Physiol Nutr Metab. 2007; 32(3):576–582. DOI: 10.1139/h07-025 [PubMed: 17510699]

Cameron FJ, Donath SM, Baghurst PA. Measuring glycaemic variation. Curr Diabetes Rev. 2010; 6(1): 17–26. [PubMed: 20214595]

Ceriello A, Novials A, Ortega E, La Sala L, Pujadas G, Testa R, … Giugliano D. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. Diabetes. 2012; 61(11):2993–2997. DOI: 10.2337/db12-0224 [PubMed: 22891214]

Desjardins K, Brazeau AS, Strychar I, Rabasa-Lhoret R. Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes? Diabetes Obes Metab. 2014; 16(7):577–587. DOI: 10.1111/dom.12232 [PubMed: 24320159]

Di Battista AM, Hart TA, Greco L, Gloizer J. Type 1 diabetes among adolescents: reduced diabetes self-care caused by social fear and fear of hypoglycemia. Diabetes Educ. 2009; 35(3):465–475. DOI: 10.1177/0145721709333492 [PubMed: 19321802]

Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. Journal of Pediatrics. 1994; 125:177–188. [PubMed: 8040759]

Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, Cox DJ. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care. 2011; 34(4):801–806. DOI: 10.2337/dc10-1343 [PubMed: 21346182]

Gonder-Frederick LA, Vajda KA, Schmidt KM, Cox DJ, Devries JH, Erol O, … Snoek FJ. Examining the Behaviour subscale of the Hypoglycaemia Fear Survey: an international study. Diabet Med. 2013; 30(5):603–609. DOI: 10.1111/dme.12129 [PubMed: 23324032]

Green L, Feher M, Catalan J. Fears and phobias in people with diabetes. Diabetes Metab Res Rev. 2000; 16(4):287–293. [PubMed: 10934458]

Hanna KM, Weaver MT, Stump TE, Fortenberry JD, DiMeglio LA. The Relationship of Worry About Hypoglycemia With Diabetes-specific and Typical Youth Behavior Among Emerging Adults With Type 1 Diabetes. Diabetes Educ. 2014; 40(4):533–542. DOI: 10.1177/0145721714528997 [PubMed: 24676275]

Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. Neuropsychopharmacology. 2010; 35(1):136–146. DOI: 10.1038/npp.2009.121 [PubMed: 19710632]

Hendrieckx C, Halliday JA, Bowden JP, Colman PG, Cohen N, Jenkins A, Speight J. Severe hypoglycaemia and its association with psychological well-being in Australian adults with type 1 diabetes attending specialist tertiary clinics. Diabetes Research and Clinical Practice. 2014; 10(3): 430–436. DOI: 10.1016/j.diabres.2013.12.005

Hill NE, Campbell C, Buchanan P, Knight M, Godsland IF, Oliver NS. Biochemical, Physiological and Psychological Changes During Endurance Exercise in People With Type 1 Diabetes. J Diabetes Sci Technol. 2016; doi: 10.1177/1932296816671956

Kildegaard J, Christensen TF, Hejlesen OK. Sources of glycemic variability--what type of technology is needed? J Diabetes Sci Technol. 2009; 3(4):986–991. [PubMed: 20144350]

Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia. 2007; 50(12): 2553–2561. DOI: 10.1007/s00125-007-0820-z [PubMed: 17882397]

Landau S, Stahl D. Sample size and power calculations for medical studies by simulation when closed form expressions are not available. Stat Methods Med Res. 2013; 22(3):324–345. DOI: 10.1177/0962280212439578 [PubMed: 22491174]

Lascar N, Kennedy A, Hancock B, Jenkins D, Andrews RC, Greenfield S, Narendran P. Attitudes and barriers to exercise in adults with type 1 diabetes (T1DM) and how best to address them: a qualitative study. PLoS One. 2014; 9(9):e108019.doi: 10.1371/journal.pone.0108019 [PubMed: 25237905]

Lawton J, Rankin D, Cooke DD, Elliott J, Amiel S, Heller S. Self-treating hypoglycaemia: a longitudinal qualitative investigation of the experiences and views of people with Type 1 diabetes. Diabet Med. 2013; 30(2):209–215. DOI: 10.1111/dme.12007 [PubMed: 22946549]

Martyn-Nemeth P, Quinn L, Hacker E, Park H, Kujath AS. Diabetes distress may adversely affect the eating styles of women with type 1 diabetes. Acta Diabetol. 2014; 51(4):683–686. DOI: 10.1007/s00592-014-0575-1 [PubMed: 24615054]

McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. Diabetes Technol Ther. 2005; 7(2):253–263. DOI: 10.1089/dia.2005.7.253 [PubMed: 15857227]

Nixon R, Pickup JC. Fear of hypoglycemia in type 1 diabetes managed by continuous subcutaneous insulin infusion: is it associated with poor glycemic control? Diabetes Technol Ther. 2011; 13(2): 93–98. DOI: 10.1089/dia.2010.0192 [PubMed: 21284474]

Pinsker JE, Kraus A, Gianferante D, Schoenberg BE, Singh SK, Ortiz H, … Kerr D. Techniques for Exercise Preparation and Management in Adults with Type 1 Diabetes. Can J Diabetes. 2016; doi: 10.1016/j.jcjd.2016.04.010

Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes. 2003; 52(11):2795–2804. [PubMed: 14578299]

Riaz M, Basit A, Fawwad A, Yakoob Ahmedani M, Ali Rizvi Z. Factors associated with non-adherence to insulin in patients with type 1 diabetes. Pak J Med Sci. 2014; 30(2):233–239. [PubMed: 24772118]

Richmond J. Effects of hypoglycaemia: patients' perceptions and experiences. Br J Nurs. 1996b; 5(17): 1054–1059. DOI: 10.12968/bjon.1996.5.17.1054 [PubMed: 8918765]

Savard V, Gingras V, Leroux C, Bertrand A, Desjardins K, Mircescu H, Rabasa-Lhoret R. Treatment of Hypoglycemia in Adult Patients with Type 1 Diabetes: An Observational Study. Can J Diabetes. 2016; doi: 10.1016/j.jcjd.2016.05.008

Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, … Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013; 36(5):1384–1395. DOI: 10.2337/dc12-2480 [PubMed: 23589542]

Soupal J, Skrha J Jr, Fajmon M, Horova E, Mraz M, Skrha J, Prazny M. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. Diabetes Technol Ther. 2014; 16(4):198–203. DOI: 10.1089/dia.2013.0205 [PubMed: 24401008]

Vallis M, Jones A, Pouwer F. Managing hypoglycemia in diabetes may be more fear management than glucose management: a practical guide for diabetes care providers. Curr Diabetes Rev. 2014; 10(6):364–370. [PubMed: 25394991]

Weiner MF, Skipper FP Jr. Euglycemia: a psychological study. Int J Psychiatry Med. 1978; 9(3–4): 281–287. [PubMed: 757217]

Wu FL, Juang JH, Yeh MC. The dilemma of diabetic patients living with hypoglycaemia. Journal of clinical nursing. 2011; 20(15–16):2277–2285. DOI: 10.1111/j.1365-2702.2011.03725.x [PubMed: 21627701]

Yardley JE, Hay J, Abou-Setta AM, Marks SD, McGavock J. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. Diabetes Res Clin Pract. 2014; 106(3): 393–400. DOI: 10.1016/j.diabres.2014.09.038 [PubMed: 25451913]

Highlights

- Fear of hypoglycemia (FOH) is a barrier to attaining optimal glucose control that may trigger behaviors that contribute to greater glycemic variability in T1DM.
- Gaps in knowledge exist related to the association of FOH and glycemic variability; CGM technology allows examination of these relationships.
- Using a prospective repeated-measures design, in young adults with T1DM, findings revealed that concurrent and previous day FOH levels were associated with greater glycemic variability.
- FOH was also associated with dietary patterns and physical activity supporting the role of FOH in self-management behaviors and intra-day glycemic variability.

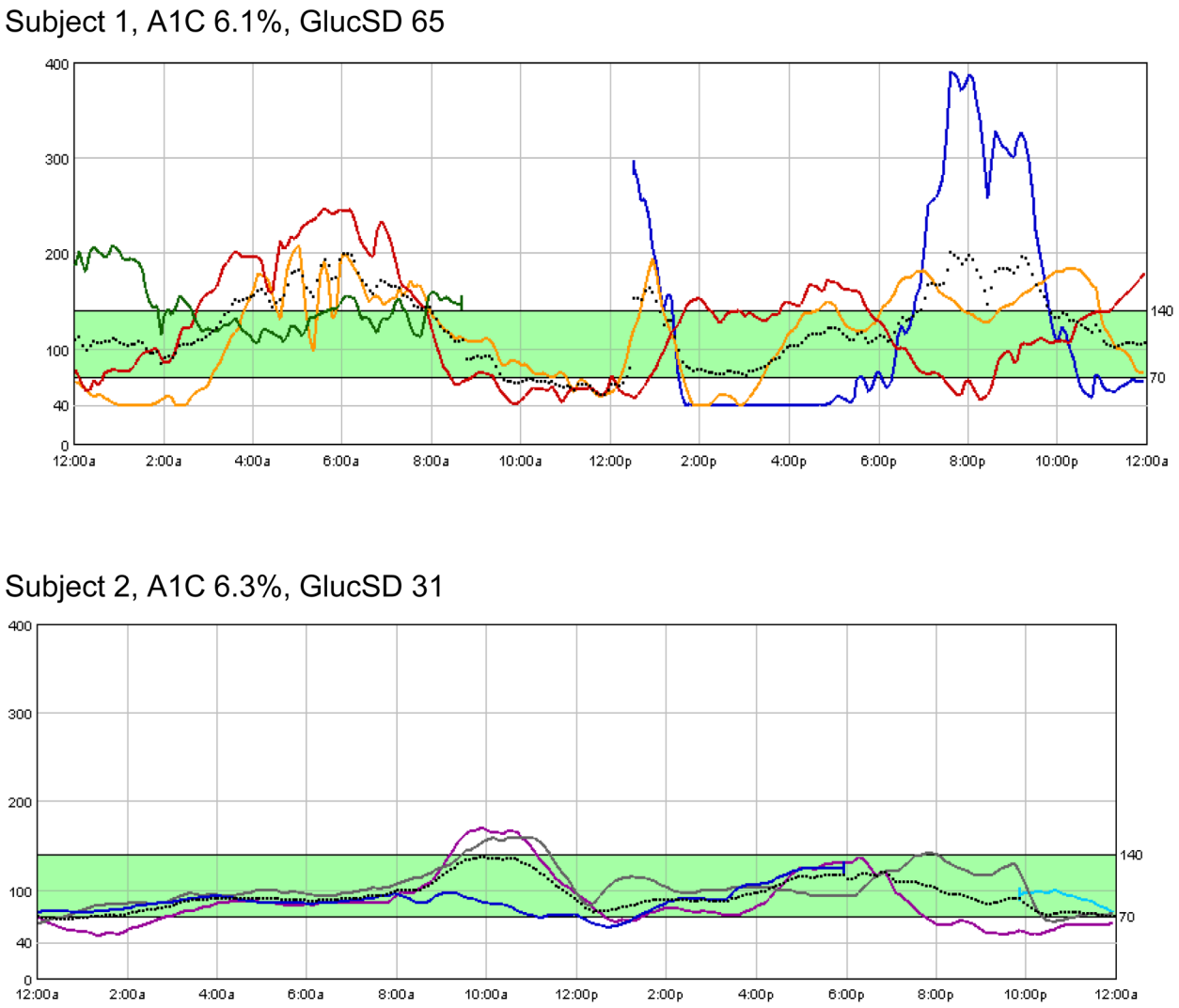

Figure 1.

3-Day CGM recordings on two subjects. Each line represents a different day. Note that, despite similar A1C levels, the GlucSDs differ.

Table 1

Baseline and Daily Measures, $N = 35$

Measure	Median	IQR	Mean	SD	Range
Demographic and Health					
Age (yrs.)			26	4	18–35
Diabetes duration (yrs.)			13	8.1	1–31
Fear of Hypoglycemia					
Baseline trait FOH (HFS worry scale)			26.6	12.4	5–52
Daily FOH (diary)					
Morning worry	2.0	2.0–3.0	2.3	1.1	1–5
Evening worry	2.0	1.0–3.5	2.3	1.2	1–5
Glycemic Measures					
Hypoglycemia					
Hypoglycemia history					
Frequency hypoglycemia/week *	3	2–7			0–25
Hypoglycemic diary (frequency/day)	1	0–1			0–4
CGM-derived hypoglycemia (hrs)	1	0–3.3			0–9.8
CGM-derived hypoglycemia (%)	5	0–15			0–66
Glycemic Variability					
CONGA-3 hr	69	49–86			17–217
CONGA-4 hr	75	53–92			16–230
CONGA-6 hr	21	14–28			16–234
Glucose-SD	34	23–53			8–149
Glycemic Control					
A1C (%)			7.2	1.0	5.1–9.8
Self-Management Behavior					
Diet					
Block Dietary Intake					
CHO (%)			43	5.7	33–52
Protein (%)			16	2.9	11–24
Fat (%)			39	4.9	30–50

J Diabetes Complications. Author manuscript; available in PMC 2018 April 01.

Measure	Median	IQR	Mean	SD	Range
Pump Record Daily CHO intake (g)	147	102–215			20–490
Medication					
Pump Record Daily insulin (U/kg)	0.6	0.4–0.7			0.2–1.5
Activity (actigraphy)					
Sedentary time (hrs)	16.9	4.3–18.6			0–23.4
Light activity (hrs)	3.9	2.8–5.3			0–10.3
Moderate activity (hrs)	1.5	0.9–2.3			0–7.3
Vigorous activity (hrs)	0.26	0–0.2			0–6.5

* < 70 mg/dl/week

Table 2

Linear Mixed Models to Estimate Associations of FOH with GV and Self-Management Behaviors * *N* = 35

	Same-Day Morning Worry			Previous-Evening Worry		
Parameter	**Estimate**	**Std. error**	***p***	**Estimate**	**Std. error**	***p***
Glycemic Variability						
CONGA3	3.92	2.28	.088	**4.41**	2.05	**.034**
CONGA4	**6.20**	2.48	**.014**	**4.60**	2.25	**.043**
CONGA6	**7.36**	2.68	**.007**	4.09	2.46	.098
GlucSD	**4.57**	1.78	**.011**	**4.40**	1.61	**.007**
Self-Management						
CHO intake	−2.34	5.42	.666	−4.76	5.07	.350
Total insulin dose/kg	−.015	.01	.134	−.009	.009	.335
Total physical activity	.101	.118	.393	−.171	.108	.115
Light activity	.005	.138	.972	−.083	.125	.505
Moderate activity	.093	.087	.287	−.089	.079	.264
Vigorous activity	−.006	.052	.908	−.082	.049	.098

* controlled for age, gender, diabetes duration, diary-derived hypoglycemia, A1C

Table 3

Overall Linear Mixed Model to Estimate Daily Factors Influencing Glycemic Variability (GlucSD), $N = 35$

Parameter	Estimate	Std. Error	*t*	Significance	Lower bound 95% confidence interval	Upper bound 95% confidence interval
Gender	3.8367	6.101	0.629	.536	−878	16.46
Age	−1.8475	0.834	−2.217	.037	− 3.57	− 0.12
Diabetes duration	1.0937	0.477	2.292	.031	0.11	2.08
A1C	1.5525	2.817	0.555	.587	−4.26	7.36
Hypoglycemic events	2.9627	2.171	1.365	.175	−1.34	7.27
Morning FOH	4.3641	2.008	2.174	.032	0.38	8.35
Physical activity (daily time spent)	2.2031	1.4323	1.538	.127	−0.64	5.04
CHO (daily intake in g.)	−0.0893	0.030	−2.986	.004	−0.15	−0.03
Total daily insulin dose, u/kg	23.1415	11.841	1.954	.058	−0.82	47.01

*controlled variables: gender, age diabetes duration, diary-derived hypoglycemia, A1C