UNIVERSITY OF CALIFORNIA SAN DIEGO

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Continuous Glucose Monitoring and Diabetes Management Behaviors: A Secondary Data Analysis from the REPLACE-BG Trial

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Public Health (Health Behavior)

by

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2018

The Dissertation of Margaret Anne Crawford is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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2018

DEDICATION

To Timbo, Muir, the mountains, and the waves.

EPIGRAPH

The greater the light within, the brighter it burns on a dark night.

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LIST OF ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes Trial
ADA	American Diabetes Association
AID	Automated insulin delivery
ANOVA	Analysis of variance
BGM	Fingerstick blood glucose meter
BMI	Body mass index
CGM	Continuous glucose monitor
CGM+BGM	CGM plus fingerstick glucose monitoring
CI	Confidence interval
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
EDIC	Epidemiology of Diabetes Interventions and Complications study
EFA	Exploratory factor analysis
FDA	Food and Drug Administration
HFS	Hypoglycemia Fear Survey
HFS-B	Hypoglycemia Fear Survey- Behavior scale
IQR	Interquartile Range
IRT	Item response theory
IU	International Unit
OCC	Option characteristic curve
RBG	REPLACE-BG trial
RMSEA	Root mean square error of approximation

SD	Standard deviation
SRMR	Standardized root mean square residual
T1D	Type 1 diabetes
T1D(s)	Person/ people with type 1 diabetes
TLI	Tucker Lewis Index

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ABSTRACT OF THE DISSERTATION

Continuous Glucose Monitoring and Diabetes Management Behaviors:
A Secondary Data Analysis from the REPLACE-BG Trial

by

Margaret Anne Crawford

Doctor of Philosophy in Public Health (Health Behavior)

University of California San Diego, 2018
San Diego State University, 2018

Professor John P. Pierce, Co-Chair
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Background: Continuous glucose monitors (CGM) are becoming a norm for type 1 diabetes management and provide the opportunity to describe hypoglycemic and hyperglycemic events experienced by people with type 1 diabetes (T1Ds). This dissertation had four objectives: 1) derive scales from the Hypoglycemia Fear Survey- Behavior (HFS-B) scale that represent unique constructs of hypoglycemia- related behavior, 2) describe the frequency and severity of CGM- measured hypoglycemic events, and assess how these relate to levels of hypoglycemia-related behaviors, 3) develop severity categories for CGM- measured hyperglycemic events and

describe how the severity categories relate to A1C, and 4) collate insulin pump and CGM data to describe how participants at different levels of A1C use insulin boluses to manage their hyperglycemic events.

Methods: Four analyses were conducted using CGM, insulin pump, demographic, and HFS-B data collected over 26 weeks from 216 T1Ds in the REPLACE-BG trial. The first was a psychometric analysis of the HFS-B. The second identified and measured hypoglycemic events and assessed how these events related to hypoglycemia-related behaviors. The third identified hyperglycemic events, categorized them by severity, and assessed how measures of hyperglycemic event severity predict A1C, the standard measure of glucose control. The fourth identified hyperglycemic events in which insulin boluses were administered and assessed the association of proactive insulin bolusing with the occurrence of severe hyperglycemic events.

Results: Three scales were derived from the HFS-B, labelled hypoglycemia avoidance, reaction, and prevention behavior. Higher levels of hypoglycemia prevention behavior were associated with a lower percentage and shorter duration of moderate hypoglycemic events. Four categories of hyperglycemic event severity were developed, and those in the best glucose control (A1C $\leq$ 7.1) had 1) a larger percent occurrence of non-severe hyperglycemic events and 2) a smaller percentage of time in the most severe event category. Finally, those in the best glucose control were more likely to practice proactive bolusing to prevent severe hyperglycemic events.

Conclusion. This analysis demonstrated the importance of CGM data in its continuous form. CGM identifies behaviors associated with prevention of both hypo- and hyperglycemia, which are preferentially performed by those with the best glucose control.

CHAPTER 1:

INTRODUCTION & SPECIFIC AIMS

Over a million people in the United States have type 1 diabetes, a disease in which the body has lost the ability to produce insulin and patients must actively regulate their blood glucose levels. Less than a third of adults with type 1 diabetes (T1D) successfully manage their diabetes according to American Diabetes Association (ADA) guidelines.[1] Uncontrolled diabetes occurs when glucose levels are consistently out of the recommended range, and is associated with later severe health consequences like liver failure, kidney failure, blindness, and limb amputation.[2] Type 1 diabetes requires daily management of glucose levels through insulin injections, self- monitoring glucose levels, physical activity, and food choices. Glucose levels, which are not readily observable, are also impacted by environmental and physiological factors, like altitude, stress, and fatigue. To successfully manage their glucose levels, patients must first monitor them, and then engage in a series of glucose management behaviors which need to be adapted to their idiosyncratic glucose responses to environmental and physiological factors.

Continuous glucose monitors (CGMs) passively measure glucose levels every 5 minutes; provide a continuous visualization of patients' glucose levels, annotated with direction and rate of change; and sound alarms to alert patients when their glucose is out of the specified range or rapidly changing. Continuous glucose monitoring is a new and innovative technology that has been on the consumer market for about ten years. Prior to this, glucose monitoring required intermittent finger pricking to obtain a blood sample that could be read photometrically. Another important innovation in diabetes management in the past few decades has been the insulin pump, which is continuously connected to a T1D's body, provides an adjustable infusion rate of basal insulin, and records the time and volume of insulin boluses that the T1D instructs the pump to

deliver. Prior to the introduction of the insulin pump, T1Ds injected insulin by filling a disposable syringe and injecting themselves. In studies that test the impact of CGM on glucose management, participants who wear CGM have improvements in A1C, average glucose, quality of life, and time spent in hypoglycemia.[3,4] Patients who wear CGM report the utility of observing their glucose values and trends in real-time, which allow for insights on how variations of food, physical activity, insulin dosing, and physiological idiosyncrasies impact their glucose.[5]

The REPLACE-BG dataset contains CGM data over a six-month period for over 200 participants, all of whom were chosen because they were considered to have well controlled diabetes. The REPLACE-BG dataset is innovative and unique in that it provides both CGM and insulin pump data for a six-month period, allowing for the assessment of insulin dosing as related to glucose values. CGM provides a significant amount of data which can be analyzed for glucose patterns, which represent glucose levels and trends that people with diabetes observe and respond to in their routine diabetes management. Most CGM- related research reports the A1C (a measure of average glucose control over previous few months) benefits of CGM and glucose metrics from aggregated CGM data,[3,4,6] but does not evaluate CGM data in its continuous form. However, the power of CGM is that it provides continuous glucose data to individuals who need to make moment to moment decisions on glucose management.

The ADA bases their guidelines for diabetes management on A1C--- while A1C is an established metric and useful for predicting risk of complications,[7] it does not describe the hyperglycemic and hypoglycemic events that inevitably occur during the management of type 1 diabetes. By measuring glucose every five minutes, CGM provides T1Ds with vital real-time data on their glucose values and trends. CGM data can be used retrospectively to reflect on behavioral explanations for glucose levels and to describe and predict time spent outside of the

optimal glucose range. By studying these patterns, we can characterize T1Ds who are able to utilize glucose management techniques to minimize hyper- or hypoglycemic events. The combination of CGM and insulin pump data provides an excellent evaluation platform for studying the effectiveness of different approaches to glucose management.

Specific Aims

Specific Aim 1

To understand which items from the Hypoglycemia Fear Survey- Behavior (HFS-B) scale are useful for measuring currently promoted diabetes management behaviors, and to derive scales that measure unique hypoglycemia-related behavior constructs.

Hypothesis 1: *The HFS-B will measure more than one domain of hypoglycemia-related behavior.*

Specific Aim 2

To describe the frequency and severity of hypoglycemic events in a group of people with well-controlled type 1 diabetes, and relate these measures to scores on hypoglycemia- related behavior scales.

We will classify hypoglycemic events based on minimum glucose value reached during the event--- mild events have a minimum value <70 mg/dL but > 50 mg/dL, moderate events have minimum values $\leq$ 50 mg/dL. Our primary outcome variables (separate models) will be 1) the percent of all hypoglycemic events that are moderate and 2) the duration of moderate hypoglycemic events. Our predictor variables will be scores on hypoglycemia avoidance, prevention, and behavior scales, which were derived from the HFS-B as part of Specific Aim 1.

Hypothesis 2: *Participants who score lower versus higher on the hypoglycemia prevention behavior scale will experience a higher percentage of moderate hypoglycemic events and a longer duration of moderate hypoglycemic events.*

Specific Aim 3

Develop categories of severity for hyperglycemic events and describe how measures of hyperglycemic events predict A1C levels.

We will classify hyperglycemic events based on duration and maximum glucose value reached during the event, using American Diabetes Association guidelines to formulate our thresholds for event severity.

Hypothesis 3: *Participants at higher levels of A1C will experience more frequent hyperglycemic events and a higher percent of total hyperglycemic events that are severe.*

Specific Aim 4

Collate insulin pump data and CGM data to describe how participants at different levels of A1C use insulin boluses to manage hyperglycemic events.

Hypothesis 4: *We hypothesize that participants with lower A1C levels will be more likely to administer insulin boluses during non-severe hyperglycemic events.*

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CHAPTER 2:

BACKGROUND AND DESCRIPTION OF DATA SOURCE

Continuous Glucose Monitoring and Glucose Measurement

People with type 1 diabetes (T1D) are told to manage their diabetes according to guidelines set forth by the American Diabetes Association (ADA) for A1C and glucose levels.[1] A1C is the established standard measurement for glucose control. It involves a simple venipuncture blood draw with a relatively inexpensive analysis that provides an acceptably accurate measure of glucose values over the past three months. Continuous glucose monitoring (CGM) involves the insertion of a sensor under the skin to provide glucose readings every 5 minutes, which was a significant technological improvement for those who need to make moment-to-moment glucose management decisions. CGM records a patient's glucose value every five minutes and transmits the glucose value to a smartphone app or receiver, which has software to allow visualization of trends in the person's glucose values. CGM delivers targeted and proximal feedback that allows the evaluation of recent glucose management practices. This is a significant advance on the single reading obtained every 3 months from regular A1C readings.

Current research practice for quantifying CGM data reports glucose metrics that are aggregated over a time period for average glucose, the percent of time spent in different glycemic categories, and the coefficient of variation of glucose.[2,3] However, the continuous data allows for more detailed characterization of glucose, such as how glucose changes over time and quantifying metrics of when the individual crosses key thresholds for both hypoglycemia and hyperglycemia. Rather than describing a person's average glucose over a period of time, these metrics describe how frequently the person experiences hypoglycemic and hyperglycemic

events, the duration of each glycemic event, and their most extreme glucose values. The following sections describe how current diabetes knowledge can be enriched through the analysis of CGM data, addressed in topical order of this dissertation.

Hypoglycemia

A hypoglycemic event is defined as any period of time that an individual has a glucose level <70 mg/dL. Glucose levels between 70 and 55 mg/dL are defined as mild hypoglycemia and glucose levels <55 mg/dL are defined as moderate hypoglycemia. If the hypoglycemic event is not arrested, the hypoglycemic event can become severe, defined as glucose levels below 35 or 40 mg/dL and requiring assistance from another individual to treat the low glucose levels. Not all T1D experience symptoms of hypoglycemia, but mild and moderate hypoglycemia can be characterized by symptoms such as sweating, shakiness, and low mental acuity; severe hypoglycemia is characterized by loss of consciousness, seizures, and death.[4–6] Mild hypoglycemic events occur regularly in T1D,[4,5,7,8] and their frequency and severity are associated with decreased psychological well-being and diabetes-related quality of life[6,9] and increased healthcare costs.[6,10] People with diabetes are encouraged to manage their glucose above 70 mg/dL and to be prepared to implement glucose management to counter hypoglycemia.

Hyperglycemia

A hyperglycemic event is defined as occurring when a T1D's glucose levels increase beyond 180 mg/dL. While hyperglycemic events are not associated with the same dire symptoms that occur in hypoglycemic events, long term tissue exposure to hyperglycemia is associated with microvascular and macrovascular complications of diabetes, such as retinopathy, neuropathy, nephropathy, coronary artery disease, and stroke.[11–15] These consequences are associated with the major health care costs associated with diabetes. In the Diabetes Control and

Complications Trial and follow-up Epidemiology of Diabetes Interventions and Complications study (DCCT/ EDIC),[16] and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[17] there was a continuous gradient between higher A1Cs (i.e.. greater exposure to hyperglycemia) and serious long term complications.

The American Diabetes Association (ADA) recommends that people with type 1 diabetes maintain their blood glucose levels between 70 and 180 mg/dL, called euglycemia, with a goal of minimizing later complications by maintaining their regular A1C below 7%[18] for most people. However, aggressive management to keep A1Cs close to the non-diabetic range (<6.5mg/dl) is often associated with more hypoglycemic events, particularly when the individual does not have access to frequent blood glucose readings.[4,5,19] Prior to the development of CGM technology, access to frequent blood glucose readings meant fingerprick testing 4-6 times a day.

CGM Alarms

The CGM sensor is a hair-thin wire that sits just under the skin, passively measures glucose every 5 minutes, and sends a continuous datastream of glucose levels to a user's smartphone or receiver via a thin transmitter that sits atop the sensor (also attached to the body). The data delivered in real-time to a T1D includes their current glucose level, the direction and rate of change of glucose, alarms that sound when glucose moves beyond pre-set thresholds, and a continuous visualization of their glucose levels over the past 24 hours. Hyperglycemia alarms are pre-set to sound when a person's glucose becomes greater than 180 mg/dL; hypoglycemia alarms are pre-set to sound when a person's glucose becomes less than 70 mg/dL, and again when their glucose is below 55 mg/dL (labelled an "urgent low glucose alarm"). Additionally, alarms will repeat if glucose has been out of range for a designated period of time--- typically over 30 minutes for hypoglycemic levels and over 2 hours for hyperglycemic levels. The 180

mg/dL and 70 mg/dL alarms and time period before repeating can be configured to an individual's preferences; the 55 mg/dL alarm is non-configurable, as it is alerting to impending severe hypoglycemia.

Hypoglycemia Reduction with CGM Wear

In the recent DIAMOND study,[20] participants with type 1 diabetes who wore CGM for six months significantly increased their time in euglycemia over the study period, while significantly decreasing the amount of time they spent in hypoglycemia. Similarly, a study that investigated the impacts of CGM alarms on glucose management found that participants (n=35) who received CGM alarms during hypoglycemic events reduced the amount of time spent in hypoglycemia (p=0.03) compared to controls (n=36) who received CGM data without alarms.[21]

Hypoglycemia Fear

Particularly in the time before CGM technology, the aversive consequences of hypoglycemic events led some T1Ds to develop hypoglycemia fear (HF) which became a barrier to optimal glucose management[22,23] as they would try to avoid having blood glucose readings at the lower end of the euglycemic range. When blood glucose levels are somewhat volatile, HF can result in T1Ds targeting the upper portion of the euglycemic range which often also leads to more time spent in hyperglycemia.[19,24,25] The Hypoglycemia Fear Survey (HFS)[22] was developed in the 1980s and it contained two sub-scales: a *Behavior subscale* and a *Worry* subscale. Changes since then, including the introduction of CGM, have made many of the items out of date. However, the Behavior Subscale (HFS-B) includes information of a person's likelihood for performing behaviors that impact glucose levels, some of which are key to preventing hypoglycemia. We utilize the HFS-B in our analyses.

Enrichment from CGM

Analyzing CGM data in its continuous form can enhance current knowledge of hypoglycemia and hypoglycemia- related behaviors by quantifying the frequency, duration, and severity of hypoglycemic events. By understanding what percent of all hypoglycemic events are moderate (< 50 mg/dL), we can address our research hypotheses on how hypoglycemia- related prevention behaviors relate to how people respond to CGM- delivered hypoglycemia alarms.

Glucose Optimization with CGM Wear

In the recent DIAMOND trial,[20] which tested for differences in glucose outcomes over time between participants who wore CGM (n=105) versus those who did not (n=53), participants who wore CGM reduced their A1C by 1.1% (0.7) within 12 weeks and sustained this reduction over the 24-week study period. This reduction in A1C was significantly greater than the control group, who had an average A1C reduction of 0.5% (0.7) that was also sustained between 12- and 24- weeks. The A1C reduction over time within the CGM group corresponded to a significant decrease in daily minutes spent in hyperglycemia (assessed as minutes >180 mg/dL, >250 mg/dL, and >300 mg/dL) between baseline and 12- and 24-weeks, and as compared to the control group. Similarly, the recent GOLD trial[26] used a crossover randomized clinical trial to assess changes in A1C during CGM wear in two different participant groups (n= 69, n=73; mean (SD) A1C 8.7% (0.8)), found that A1C was reduced by 0.43% after a CGM wear period, compared to during non-CGM wear periods. While it can be assumed that these participants reduced the amount of time spent in hyperglycemia, the GOLD trial did not report time spent in glycemic ranges.

Insulin Administration for Glucose Management

The American Diabetes Association recommends that people with diabetes manage their glucose through insulin dosing, food choices, and physical activity.[18] However, these are like three simultaneous equations that are impossible to optimize without controlling one of the variables. In this study, we do not have information on either the timing or the content/quality of food intake, nor were the participants wearing physical activity measurement devices. However, all were wearing insulin pumps which record insulin doses over time. Accordingly, we limit our study of glucose management decisions to the use of insulin boluses. An insulin bolus is a dose of fast-acting insulin administered *proactively* to treat hyperglycemia that is expected to come with food intake, and *reactively* to reduce blood glucose and escape from a hyperglycemic event. By facilitating more frequent monitoring of glucose and delivering alarms for hyperglycemia, CGM facilitates more opportunities for a person to observe and respond to glucose values that are discrepant with their personally optimal glucose range--- a number of guides have been developed (for both health professionals and T1Ds) for best management practices for different CGM scenarios.[27–31]

Enrichment from Insulin Pump and CGM Data

For any given hyperglycemic event during this study, we know when the CGM triggered an alarm indicating the need for a management decision. Using this alarm as a starting point, we are able to calculate when each T1D decided that it was necessary to give an insulin bolus to drop their glucose back into the euglycemic range, as well as the size of the bolus relevant to usual insulin intake. As hyperglycemic events are a highly prevalent event, we have replicate data on individuals which can help us develop meaningful patterns of dosing across the study.

Behavioral Theory of How CGM Impacts Glucose Management Behavior

CGMs provide a visualization of continuous glucose values that highlight temporal patterns in patients' glucose fluctuations. Alarms attached to crossing high and low glucose thresholds act as "cues to action" to implement glucose management behaviors. A person's previous history of success and/or difficulty in applying behavioral solutions to optimize glucose levels impacts their self-efficacy and confidence that they can be successful in future management. When a person acts, they evaluate the outcome of that action through a self-reflection process (Figure 2.1) and a self-regulation process (Figure 2.2), constructs of the Social Cognitive Theory. In this study, CGM use with alerts that are "cues to action" are expected to produce different responses among T1Ds with different histories of good glucose management (i.e. A1C levels) and we expect that diabetes self-management decisions will be mediated by their use of self-reflection, self-regulation, and control theory responses.

CGM and Self Reflection

Patients create personalized diabetes management goals that evolve over time based on feedback from their doctors, evolving personal health requirements, and, most importantly, based on past experiences managing their diabetes. In the self reflection process, a person compares their current glucose values to their existing standards for glucose control. This process works constructively when a person consistently performs adequately (or better) and thus raises her performance standards, creating a feedback loop of progress and continual motivation. Alternatively, this can work negatively if a person regularly fails to meet her glucose management goals. In this case, the person might set lower standards or lose motivation to self-monitor and act in response to the "cues for action".

CGM and Self-Regulation

The self-regulation process includes a person's self-judgment on whether they deserve incentives for their performance, and this is influenced by the quality of their self-observation, judgment, and self-reaction.[32(335)] The effortless access to glucose values and "cues to action" provided by CGM is consistent with the three components of successful self-observation described by Bandura: "fidelity, consistency, and temporal proximity."[32(337)] Reading glucose values in real-time allows the patient the opportunity to both observe her glucose and adjust her glucose management behaviors within a proximal time period.

Past CGM data serves as a reference for judging ongoing performance and shapes the patient's internal standards for the glucose management that they can achieve. Since a patient's daily behaviors impact their glucose values and aggregate over time, a patient's A1C is determined by their habitual behaviors. Even those who have good glucose management skills will have several periods each day when their glucose moves to levels that require management action to return to euglycemia.

CGM Alarms and Control Theory

While the social cognitive theory of self-regulation described above explains the long-term effects of CGM on glucose management, control theory explains the momentary self-regulatory process patients experience when evaluating their glucose. The control theory accounts for the discrepancy- reducing feedback loop that occurs within the judgmental process.[33] If the patient's glucose is outside of the referent range, then the patient examines the lower level components of their glucose management to understand why there is a discrepancy between their present glucose value and their internal standards for glucose values, and corrects their actions accordingly.[33]

The function of hyperglycemic and hypoglycemic alarms is to draw the patient's attention to the *self*.[33] CGM alarms interrupt the patient's current activity and focus, indicate the patient's need for immediate glucose management intervention, and allow diabetes management behaviors to come to the forefront of the patient's attention. Our analyses include evaluating the percentages of total hyperglycemic and hypoglycemic events that are mild and moderate, which may indicate a T1D's inattentiveness to responding to alarms related to mild hyperglycemic and hypoglycemic events in order to prevent progression to moderate events. This may also indicate low self-efficacy or lack of knowledge about good glucose management skills. Our hypothesis is that those T1Ds who have better A1Cs will make quicker and more decisive decisions (i.e. larger insulin bolus volumes) when faced with rapidly increasing glucose levels during an hyperglycemic excursion.

Data Source

The data analyzed in this dissertation come from the REPLACE-BG trial (RBG)[34] that was conducted at 14 sites in the Type 1 Diabetes Exchange Clinic Network. The objective of the trial was to evaluate if CGM glucose values are safe to inform insulin bolusing decisions, compared to confirming each CGM glucose value with a fingerstick glucose value prior to insulin bolusing (the Food and Drug Administration (FDA) requirement at the time). Participants were randomized 2:1 to CGM-only (n=149) or CGM+BGM (CGM plus fingerstick monitoring, n=77). The outcomes of the trial showed no difference in glucose control between these two study groups, measured through A1C and CGM-derived time spent in glycemic ranges. Accordingly, for our study, we combine study groups since they received the same CGM data with the same alerts , and because the primary outcome paper indicated that the study had no impact on either glucose or psychosocial outcomes. In addition to wearing a CGM, participants

wore insulin pumps throughout the study, which passively recorded insulin boluses. Additionally, all participants took part in a run-in phase to build competency in using CGM glucose trends and alerts as a diabetes management tool; this run-in phase varied in length according to each participant's assessed need for training in using CGM.

Study Population

Participants were $\geq$ 18 years of age (mean 44 $\pm$ 14 years), had type one diabetes for at least one year (mean duration 24 $\pm$ 12 years), used an insulin pump, and had an HbA1c $\leq$ 9.0% (mean 7.0 $\pm$ 0.7%). Before the study, 47% of the participants were current CGM users. The study randomized 226 participants between May 2015 and March 2016.

Severe Hypoglycemia and Diabetic Ketoacidosis

Exclusion criteria included the following: a) severe hypoglycemia in the last 12 months in which the assistance of another individual was needed b) seizure/loss of consciousness in the past 3 years, c) significant hypoglycemia unawareness based on the Clarke Hypoglycemia Unawareness Survey,[35] d) more than one diabetic ketoacidosis (DKA) episode in the past year, and e) conditions related to cardiovascular health, thyroid, pregnancy, and psychiatry. Sixty-five percent of participants reported never experiencing a severe hypoglycemic episode, and the remaining participants reported not experiencing severe hypoglycemia in the past year. Seventy-four percent of participants reported never experiencing DKA, and the remaining participants reported not experiencing more than one DKA episode in the previous year. Of the 57 participants who reported experiencing DKA, only 2 participants experienced DKA in the previous year.

Study Instruments

Continuous Glucose Monitor (CGM) Data

Participants wore CGM continuously for 6 months, which recorded a glucose value every 5 minutes. Participants' CGM data will be analyzed for percentages of time spent in range (70-180 mg/dL), mild hypoglycemia (<70 mg/dL, >50 mg/dL), moderate hypoglycemia (≤50 mg/dL), hyperglycemia (>180 mg/dL), mean glucose, and measures of glucose variability (standard deviation, coefficient of variation).

Hypoglycemic and Hyperglycemic Events

Hypoglycemic and hyperglycemic events will be identified in the CGM data. We will measure the minimum or maximum value reached, duration of event, and time of event initiation. Hyperglycemic events begin when glucose becomes greater than 180 mg/dL and ends when glucose returns to below 180 mg/dL. Hypoglycemic events begin when glucose is less than or equal to 70 mg/dL and end when glucose returns to greater than 70 mg/dL.

Severity of Events

Hypoglycemic events are categorized as mild or moderate based on the minimum glucose value reached during the event. Mild hypoglycemic events have minimum glucose values <70 mg/dL but >50 mg/dL, and moderate hypoglycemic events have minimum glucose values ≤50 mg/dL (lowest recordable glucose level by CGM is 39mg/dL). Hyperglycemic events are sorted into four categories based on duration and maximum value of event. For our decision rules, we utilize the ADA definition of mild hyperglycemia (>180 mg/dL, < 250 mg/dL) and moderate hyperglycemia (>250 mg/dL),[13] in conjunction with their recommendation that meal-related hyperglycemia should last less than 2 hours.[13] We created hyperglycemic event categories by stratifying total hyperglycemic events by the duration (5 -29.9 minutes, 30-119.9

minutes, < 2 hours, or >2 hours) and a binary variable that represented if the maximum glucose value during the excursion exceeded 250 mg/dL.

Insulin Pump Data

Participants wore insulin pumps for the duration of the study. We will analyze insulin pump data for volume and timestamp of insulin boluses.

Screening Survey

Participants answered this survey during screening and provided the following information: 1) *demographic information* (age, gender, race/ethnicity, education level, annual income, source of medical insurance) and 2) *diabetes information* (duration of diabetes diagnosis, most recent severe hypoglycemia, most recent DKA, and duration of CGM use). Participants also received a physical exam during screening, which included height, weight, and either point of care or laboratory A1C.

Hypoglycemia Fear Survey (HFS)

Participants answered this 24-item survey that measures behavioral and worry dimensions of hypoglycemic fear.[22] The HFS presents 24 items and asks the participant to rate their likelihood of performing each behavior (scale from 0 to 4). Examples include: "Keep my sugar high when I will be alone for a while," "Carry fast-acting sugar with me," "I worry about passing out in public," and "I worry about feeling lightheaded or dizzy." HFS item scores will be averaged, and higher scores indicate a greater fear of hypoglycemia.[22]

Our analysis of glucose metrics within this population of people with well-controlled glucose will identify the glucose values and patterns that are typical in T1D with A1C of 7.0% $\pm$ 0.7% and a maximum of 9.0%. Until CGM, glucose management was understood on a broad level that focused on A1C- indicated average glucose, but did not take into account the granular-

level hypoglycemic and hyperglycemic events that happen multiple times throughout a day. We will categorize these regular hyperglycemic and hypoglycemic events and identify if there are different patterns depending on the A1C level of the participants.

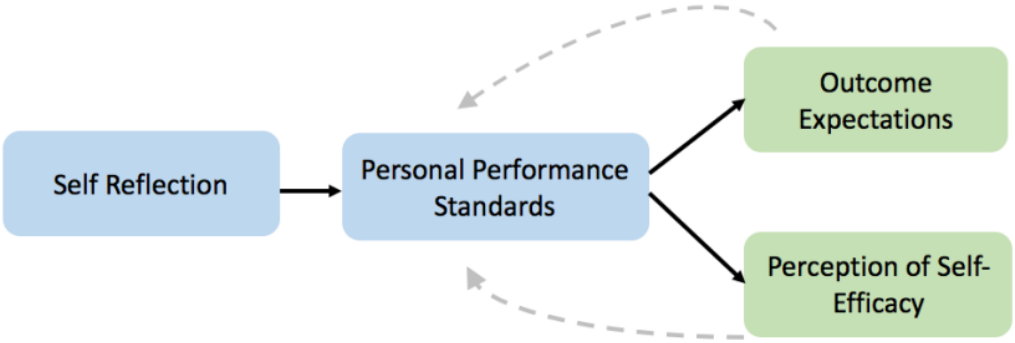

Figure 2.1: CGM and the Self Reflection Process

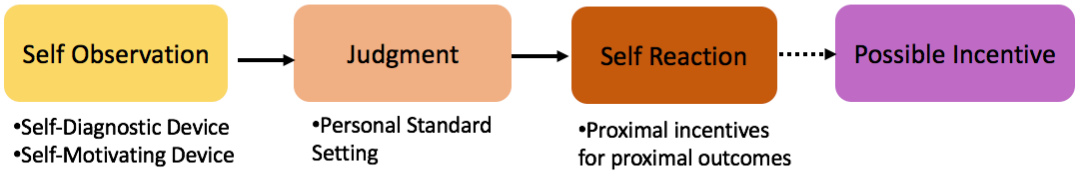

Figure 2.2: CGM in the Self Regulation Process

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CHAPTER 3:

HOW THE HYPOGLYCEMIA FEAR SURVEY MEASURES HYPOGLYCEMIA-RELATED BEHAVIOR CONSTRUCTS IN PEOPLE WITH TYPE 1 DIABETES WHO WEAR CONTINUOUS GLUCOSE MONITORS

Specific Aim: To understand which items from the Hypoglycemia Fear Survey- Behavior (HFS-B) scale are useful for measuring currently promoted diabetes management behaviors, and to derive scales that measure unique hypoglycemia-related behavior constructs.

Hypothesis: *The HFS-B will measure more than one domain of hypoglycemia-related behavior.*

Introduction

Hypoglycemia (low glucose levels in the body) is a common occurrence in diabetes management, resulting from overestimating the amount of insulin needed to treat for a given intake of carbohydrates or level of physical activity to maintain euglycemia (glucose levels 70-180 mg/dL). Hypoglycemia is often characterized by perspiration, hunger, and shakiness at mild levels (< 70 mg/dL), by sleepiness and confusion at moderate levels (< 55 mg/ dL), and can involve loss of consciousness, seizures, and death in severe cases (< 35- 40 mg/dL).[1–3] The Hypoglycemia Fear Survey (HFS) was first published in 1987,[4] was revised to its current form in 1989 (HFS-II),[5] and was designed to measure the likelihood of performing behaviors related to hypoglycemia and worrying about hypoglycemia given the status of glucose measurement and treatment at the time. The HFS is intended to be administered to adults with type 1 diabetes and is comprised of a behavior subscale (HFS-B) and a worry subscale (HFS-W).

Because the HFS was developed over 30 years ago, advances in treatment have reduced the relevance of some of its items to current norms in glucose management. For example, the item “Eating a large snack at bedtime” reflects a diabetes management behavior that is relevant

to the insulin regimens patients were prescribed in the 1980s and 1990s, but is not a currently encouraged glucose management behavior. Similarly, the items "Avoid being alone when low blood glucose is likely" and "Run my glucose high when I am alone" are both behaviors that would be likely if a person has infrequent opportunities to monitor their glucose. Recent research that assessed the psychometric properties of the HFS-II in contemporary populations found the HFS to be comprised of three factors. The HFS-W was represented by one factor (*worry*) while the HFS-B was represented by two factors, pertaining to *hypoglycemia avoidance* and *maintaining high blood glucose.*[6,7]

Continuous glucose monitoring (CGM) passively measures glucose levels every five minutes and is becoming the new norm for glucose monitoring in people with type 1 diabetes. Compared to past norms in diabetes management, which required detecting low glucose through feeling the symptoms of hypoglycemia or measuring blood glucose through fingerstick monitoring, CGM serves as a safety net for detecting and alerting people of hypoglycemia. CGM provides alerts for mild low glucose levels (<70 mg/dL) that are not immediately dangerous but should be treated to prevent progression of low glucose, and also moderate low glucose levels (<55 mg/dL) that should be treated urgently to avoid severe low glucose. Hypoglycemia alarms from CGM are particularly important to T1Ds who do not experience any symptoms of hypoglycemia, or only experience symptoms once their glucose is very low. As CGM becomes the norm for glucose monitoring, we aim to understand how HFS-B measures hypoglycemia-related behaviors in T1Ds who use CGM. We hypothesize that the HFS-B measures multiple constructs of hypoglycemia- related behaviors that pertain to avoiding, treating, and preventing hypoglycemia.

The data in this dissertation comes from the Replace-BG (RBG) trial, a study of people with type 1 diabetes who managed their diabetes with continuous glucose monitors (CGM) and insulin pumps. We utilize only the HFS-B in this analysis since our objectives pertain to understanding how participants behave to avoid, prevent, and react to hypoglycemia. In this chapter, we present the psychometric properties of the HFS-B to ensure that the behavior questions are part of the same construct. We 1) assess face validity, 2) conduct exploratory factor analysis, 3) estimate reliability, 4) estimate scalability, 5) evaluate assumptions of monotonicity, and 6) fit models based in item response theory to describe information in the HFS-B items. We hypothesize that the HFS-B measures more than one domain of hypoglycemia related behaviors in contemporary populations due to improvements in treatments and glucose monitoring technology. In this analysis, we also refine the HFS-B in preparation for future analyses that evaluate how HFS-B constructs relate to hypoglycemic events.

Methods

Sample Characteristics

The details of the RBG trial have been previously published.[8] The population is comprised of people with type 1 diabetes, 50% female, 90% white, and median (IQR) age 43.5 (31.0- 55.0) years and BMI 26.7 (24.0- 30.0) kg/m^2. Sixty-five percent of participants reported never experiencing a severe hypoglycemic event and 74% reported never experiencing diabetic ketoacidosis (resulting from chronic high glucose levels). The trial was conducted at 14 endocrinology practices in the United States that were members of the Type 1 Diabetes Exchange Network, of which 4 were community-based and 10 were academic centers.

Scale Description

The HFS-B scale that is the focus of this chapter was administered to the study participants at the end of a 6-month CGM wear period. The scale is comprised of 10 items, each of which had the following lead-in: "I am likely to…" Participants answered questions on a 5-point Likert scale with 0 indicating "never" and 4 indicating "always."

Data Analysis

To assess the face validity of the HFS-B items, we asked a number of experts in the field (diabetes endocrinologist, psychologist specializing in diabetes, person with type 1 diabetes) to review the items as related to describing hypoglycemia- related behaviors that are currently promoted diabetes management practices.

To separate the different behavioral constructs measured by the HFS-B, an exploratory factor analyses was conducted using all HFS-B questions, and testing whether, in this population, these could be differentiated into one, two, and three behavioral constructs/ factors. Additionally, the HFS-B was modeled to estimate Omega, a hierarchal reliability index, to quantify the general factor affecting each item and lower-order group factors. The number of measured constructs are also assessed through parallel analysis, which compares the analysis dataset to random datasets of the same size and compares extracted factors from each to facilitate comparison of observed eigen values in the analysis dataset to those in the comparison dataset. We plot the parallel analysis results in scree plots to visualize the number of factors that are supported before the eigen value decreased markedly.

Factor loadings were considered satisfactory if loading values were > 0.30 and there was no cross loading or freestanding items.[9] The Tucker Lewis Index (TLI) measured model fit, ranging from 0 to 1, with higher values suggesting a better fit, when comparing between

models.[10] The root mean square error of approximation (RMSEA) and standardized root mean square residual (SRMR) measure model fit, with smaller values indicating a better fit.[10] The chi-square test for the goodness of fit of the model indicates a better fit if the value is smaller.[11]

To measure the extent that all items form a coherent scale, we compute scalability; and to measure the extent that individual items increase across increasing scores on the unidimensional latent trait, we measure monotonicity. Scalability coefficients are considered weak if between 0.3 and 0.4, moderate if between 0.4 and 0.5, and strong if > 0.5.[12–14] Item response theory (IRT) methods were used to evaluate if the response options of HFS-B items measured unique levels of the latent trait.

According to findings of the HFS-B scale analysis, subscales were created to measure unique HFS-B factors. These subscales were subsequently assessed for exploratory factor analysis, confirmatory factor analysis, and reliability. In order to compare the reliability of the full HFS-B and the derived subscales, we assess internal consistency with Cronbach's alpha,[15,16] a measure of how closely the scale items measure the same construct. Considering the brevity of the scale (and subsequent subscales), Cronbach's alpha scores were interpreted as: 0.55- 0.70: acceptable; 0.70- 0.90: excellent; > 0.90: consider shortening (since an increase in number of items is mathematically related to an increase in alpha).[17]

Results

Table 3.1 summarizes the mean (SD) score for each item and lists the content of each item.

Face Validity

Items B1, B2, B3, B4, B7 were judged by the expert panel to lack face validity as relevant to current glucose management behaviors. Items B5, B6, B8, B9, and B10 were judged to have high face validity (Table 3.1).

Exploratory Factor Analysis (EFA) of HFS-B

EFA of the HFS-B indicated that there were three independent factors, with fit estimates [$X^2(217)= 42.62$, $p <0.001$; RMSEA= 0.098 (90% CI= 0.067, 0.126); (SRMR) is 0.07; TLI= 0.811]. Fit statistics were less satisfactory in a 1 factor environment [$X^2(217)= 357.7$, $p <0.001$; RMSEA= 0.178 (90% CI= 0.156, 0.195); (SRMR) is 0.15; TLI= 0.372] and in a 2 factor environment [$X^2(217)= 196.48$, $p <0.001$; RMSEA= 0.14 (90% CI= 0.115, 0.161); (SRMR) is 0.13; TLI= 0.613].

In the three-factor solution, items B1, B2, B3, B4, B7 (i.e. those considered to not have face validity) load onto the first factor, with coefficients ranging from 0.31 to 0.91. Items B5 and B6 load onto the second factor, with coefficients of 0.29 and 0.99, respectively. Items B8, B9, and B10 load onto the third factor with respective coefficients of 0.66, 0.53, and 0.52. The correlation between factors 1 and 2 was 0.00, between factors 1 and 3 was 0.16, and between factors 2 and 3 was 0.19. These results support three distinct dimensions of HFS-B, which was confirmed through parallel analysis as evidenced by three eigenvalues (values of 0.4, 1.0, and 2.1) from factor analysis that were greater than eigenvalues from the randomly generated datasets (visualized in Figure 3.1 scree plot).

Omega of HFS-B

Hierarchical factor modeling was used to estimate whether a single primary factor may organize variability identified within the three subscales suggested by the EFA. Omega

reliability, which reflects the saturation of the variance from all items by a single primary factor underlying the HFS-B was 0.40, $X^2(217)= 180.21$, $p <0.001$; RMSEA= 0.141 (90% CI= 0.119, 0.159); SRMR= 0.17. The addition of the primary factor did not alter item interrelationships significantly, as coefficients of the items had loadings similar to the three-factor EFA--- the 5 items that load onto factor 1 ranged from 0.4 to 0.6, the coefficients of both items that load onto factor 2 were 0.4, and the 3 items loading onto factor 3 ranged from 0.4 to 0.5. Scalability estimates of the full scale was weak (H=0.24), an additional sign of multiple sources of variability within this set of items. Because the three-factor solution from the EFA was best supported, HFS-B items were separated according to their assigned factor and subscales were formed.

Evaluation of Subscales

The three subscales created in response to EFA represent *hypoglycemia avoidance behavior* (items B1, B2, B3, B4, B7), *hypoglycemia reaction behavior* (items b5 and b6), and *hypoglycemia prevention behavior* (items B8, B9, B10). Table 3.1 indicates which items compose the *hypoglycemia avoidance, reaction,* and *prevention behavior* subscales. Assessment of the *hypoglycemia avoidance, reaction, and prevention behavior* subscales indicated that each subscale met the following criteria for reliability, scalability, and monotonicity:

The reliability of the *hypoglycemia avoidance behavior* subscale was 0.73 (Cronbach's alpha), scalability was moderate (H=0.41; SE= 0.04), and H of all items ranged from 0.32 to 0.49 in monotonicity analysis. Scalability and reliability indices indicated that the *hypoglycemia avoidance behavior* subscale reflects one factor reliably.

The reliability of the two-item *hypoglycemia reaction behavior* subscale was in the lower range of acceptable (Cronbach's alpha=0.49), scalability was relatively weak (H=0.37; SE=

0.07), compared to the *hypoglycemia avoidance behavior* subscale, and H of both items were 0.37 in monotonicity analysis. Scalability and reliability indices were interpreted as supporting the *hypoglycemia reaction behavior* subscale.

The reliability of the three-item *hypoglycemia prevention behavior* subscale was also in the lower range of acceptable (Cronbach's alpha=0.56), scalability was 0.36 (SE= 0.06), and H of all items ranged from 0.34 to 0.40 in monotonicity analysis. Scalability and reliability indices were interpreted as supportive of the *hypoglycemia prevention behavior* subscale.

IRT Methods

Visualization of option characteristic curves (OCCs) for the *hypoglycemia avoidance behavior* subscale indicated that the response options measured distinct levels of within the distribution of scores. For the *hypoglycemia prevention behavior* and *hypoglycemia reaction behavior* subscales, visualization of option characteristic curves indicated that all response options differentiated distinct levels well, and suggested both options 0 and 1 (*never* and *rarely)* were associated with very low levels of reaction behaviors, levels not differentiated in this sample. Upon trimming the response options, the reliability of the *hypoglycemia prevention behavior* or *hypoglycemia reaction behavior* subscales did not increase (*prevention* subscale*:* 5-option Cronbach's alpha= 0.6, 4-item Cronbach's alpha=0.6; *reaction* subscale*:* 5-option Cronbach's alpha= 0.5, 4-item= 0.5), so the original 5-option responses were maintained in further analyses. OCCs for representative items of the *hypoglycemia avoidance, prevention, and reaction behavior* subscales are visualized in Table 3.2.

Discussion

This analysis guided the formation of three HFS-B subscales that distinctly measure three dimensions of hypoglycemia-related behaviors: *hypoglycemia avoidance behavior,*

hypoglycemia reaction behavior, and *hypoglycemia prevention behavior.* The scalability (Scale H) of the *hypoglycemia avoidance behavior* subscale is 0.41, *hypoglycemia reaction behavior* scalability is 0.37 (Scale H), and *hypoglycemia prevention behavior* scalability is 0.36 (Scale H). The monotonicity of the items within the *hypoglycemia avoidance behavior* subscale range from 0.32- 0.49, the *hypoglycemia reaction behavior* items are both 0.37, and the *hypoglycemia prevention behavior* items range from 0.34 to 0.42. The reliability of the *hypoglycemia avoidance behavior* subscale was strong (Cronbach's a= 0.73) and the reliability of the *hypoglycemia reaction behavior* and *hypoglycemia prevention behavior* subscales were acceptable (Cronbach's a= 0.49, 0.56, respectively).

This analysis confirmed our hypothesis that, when administered to a contemporary population of people with type 1 diabetes who use CGM and insulin pumps, the HFS-B measures more than one domain of hypoglycemia- related behaviors. In accordance with the initial assessment of face validity, items judged as having low face validity for a construct defined by a primary fear of hypoglycemia instead loaded onto a separate factor, which became the *hypoglycemia avoidance behavior* subscale. The *hypoglycemia avoidance behavior* subscale reflected behaviors that were more likely if a person monitored their glucose infrequently or had suboptimal insulin regimens. Comparatively, the behaviors included in the *hypoglycemia reaction behavior* and *hypoglycemia prevention behavior* subscales are currently promoted diabetes management behaviors. The items in the *hypoglycemia reaction behavior* subscale, "Eat something as soon as I feel the first sign of low blood glucose," and "Reduce my insulin when I think my sugar is low" are behaviors that a person engages in once their glucose is already low. Alternatively, the items in the *hypoglycemia prevention behavior* subscale, "Carry fast-acting sugar with me," "Avoid exercise when I think my sugar is low," and "Check my sugar often

when I plan to be in a long meeting or party" are behaviors a person does before their glucose is low in efforts to prevent low glucose.

The three subscales produced by this analysis will be used in subsequent analyses that evaluate the relationship between hypoglycemia-related behaviors and hypoglycemic events. By separating the three constructs measured by the HFS-B, these subscales allow for more specific measurement of how individual hypoglycemia-related behaviors relate to hypoglycemic events. The three subscales will be included together as predictor variables in models that predict duration and frequency of severe hypoglycemic events in order to evaluate which hypoglycemia-related behavior constructs are relevant to predicting hypoglycemic events. This will further refine our understanding of how hypoglycemia-related behaviors, and how components of the HFS-B relate to hypoglycemia in a contemporary population of people with diabetes who use CGM and insulin pumps.

Because the original Hypoglycemia Fear Survey was created in 1986, the survey items could be updated to reflect representative hypoglycemia- related glucose management behaviors in a contemporary population of people with type 1 diabetes. An approach to updating the items would be to first hold focus groups of people with type 1 diabetes who use CGM in which the participants state glucose management behaviors that they engage in related to *hypoglycemia avoidance, reaction,* and *prevention.* The next step is to create a survey based on the focus group findings, with separate subscales for *hypoglycemia avoidance, reaction, and prevention behavior* constructs. Then, the survey should be administered to a small group of participants and its psychometric properties evaluated for scalability, reliability, and monotonicity. The survey should subsequently be administered to a large number of participants with a large range of glucose control (identified through CGM-measured frequency, duration, and severity of

hypoglycemia) and assessed for how the survey measures *hypoglycemia avoidance, reaction, and prevention* behaviors across the population.

The above described method would identify additional survey items that could improve the reliability and scalability of the *hypoglycemia reaction* and *prevention behavior* subscales. It would also capture currently relevant behaviors that people engage in related to *hypoglycemia avoidance behavior*. It is important to measure a person's likelihood of engaging in *hypoglycemia avoidance behavior* since these behaviors are likely to result in elevated glucose levels. By understanding if the cause of a person's elevated glucose levels is *hypoglycemia avoidance behavior*, a patient can be supported with education and psychological support to overcome this barrier to glucose management and improve their glucose outcomes.

Table 3.1: Hypoglycemia Fear Survey-Behavior (HFS-B) Scores, Face Validity, and Subscales (n=216)[a]

Item Number	Item Content	Mean (SD) Score	Face Validity	Subscale
B1	Eat large snacks at bedtime	1.4 (0.8)	Low	Avoidance
B2	Avoid being alone when my sugar is likely to be low	0.9 (1.0)	Low	Avoidance
B3	If test blood glucose, run a little high to be on the safe side	1.6 (1.0)	Low	Avoidance
B4	Keep my sugar high when I will be alone for a while	0.7 (0.8)	Low	Avoidance
B5	Eat something as soon as I feel the first sign of low blood glucose	2.7 (1.0)	High	Reaction
B6	Reduce my insulin when I think my sugar is low	2.2 (1.0)	High	Reaction
B7	Keep my sugar high when I plan to be in a long meeting	1.2 (0.9)	Low	Avoidance
B8	Carry fast-acting sugar with me	3.5 (1.0)	High	Prevention
B9	Avoid exercise when I think my sugar is low	2.8 (1.1)	High	Prevention
B10	Check my sugar often when I plan to be in a long meeting or party	2.4 (1.1)	High	Prevention
----	Total HF Behavior Subscale	1.9 (0.5)	----	----
----	HFS-B Avoidance Subscale	1.2 (0.6)	----	----
----	HFS-B Reaction Subscale	2.5 (0.8)	----	----
----	HFS-B Prevention Subscale	2.9 (0.8)	----	----

[a]All items are responded to in the context of "How likely are you to perform these behaviors?" with response options on a 0-4 scale. A response of 0 indicates "never" and 4 indicates "always."

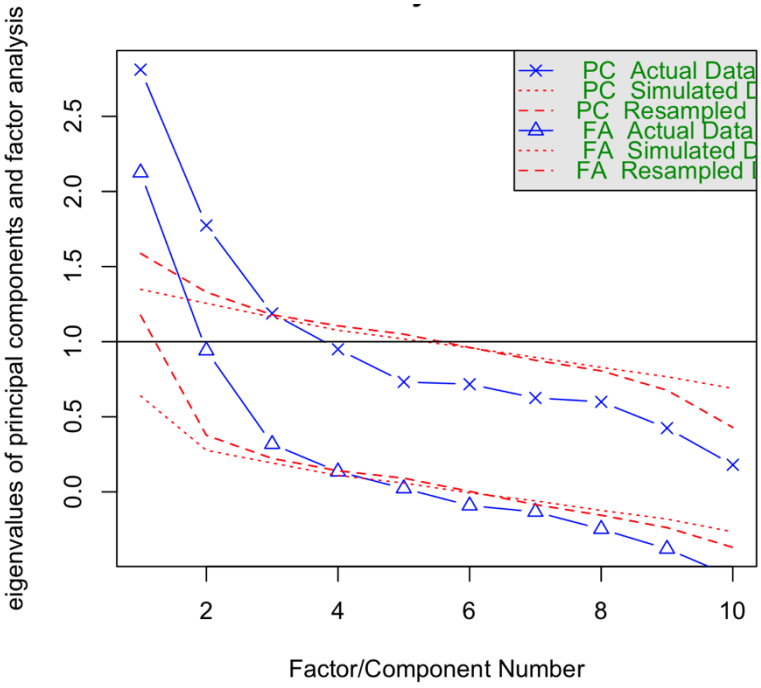
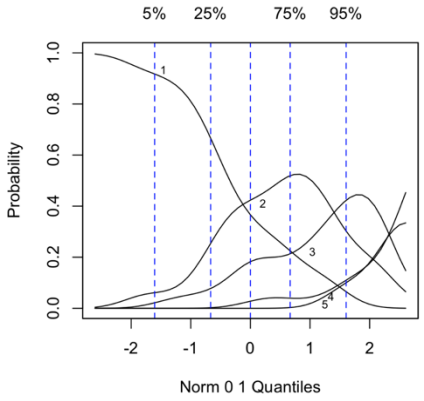
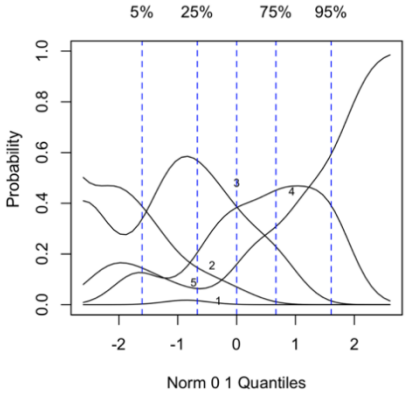
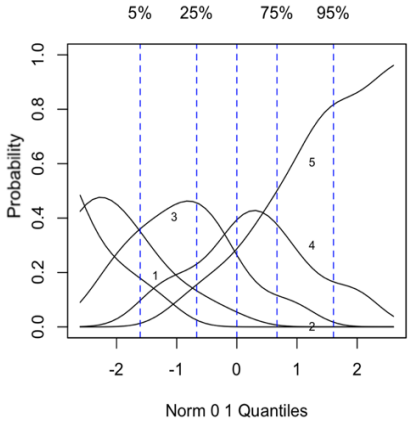


Figure 3.1: Scree Plot of HFS-B

Table 3.2: Option Characteristic Curves for Representative HFS-B Subscale Items

Hypoglycemia Avoidance Subscale <u>Item:</u> *Avoid being alone when my blood sugar is likely to be low.*	
Hypoglycemia Reaction Subscale <u>Item:</u> *Eat something as soon as I feel the first sign of low blood glucose.*	
Hypoglycemia Prevention Subscale <u>Item:</u> *Avoid exercise when I think my sugar is low.*	

[a]All items are responded to in the context of "How likely are you to perform these behaviors?" with response options on a 0-4 scale. A response of 0 indicates "never" and 4 indicates "always."

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CHAPTER 4:

THE ASSOCIATION OF CGM- MEASURED HYPOGLYCEMIC EVENTS AND HYPOGLYCEMIA BEHAVIOR CONSTRUCTS

Specific Aim: To describe the frequency and severity of hypoglycemic events in a group of people with well-controlled type 1 diabetes, and relate these measures to scores on hypoglycemia- related behavior scales.

Hypothesis: *Participants who score lower versus higher on the hypoglycemia prevention behavior scale will experience a higher percentage of moderate hypoglycemic events and a longer duration of moderate hypoglycemic events.*

Introduction

Hypoglycemic events occur regularly in many people with type 1 diabetes (T1D)[1–4] and are often characterized by perspiration, hunger, and shakiness at mild levels of hypoglycemia (<70 mg/dL), by sleepiness and confusion at moderate levels (<50 mg/ dL), and can involve loss of consciousness, seizures, and death in severe cases (< 35 mg/dL).[2,5,6] Frequent hypoglycemic events are associated with decreased psychological well-being and diabetes-related quality of life[5,7] and increased health care costs.[5,8] The American Diabetes Association (ADA) recommends that people with diabetes manage their glucose in the range of 70 and 180 mg/dL and are prepared to treat hypoglycemia by carrying fast acting sugar.[9]

Continuous glucose monitors (CGM) record a person's glucose levels in real time, providing continuous information to the person and alarms when glucose levels become hypoglycemic. The CGM alarms provide a cue to action that, if responded to quickly with fast-acting sugar, can prevent a mild hypoglycemic event (glucose <70 mg/dL and >50 mg/dL) from becoming moderate or severe.[9] Because not all people experience symptoms of hypoglycemia,

the CGM alarm for hypoglycemia is especially important in alerting T1Ds that action is required to maintain safe glucose levels. In studies of people with type 1 diabetes who wear CGM,[10–12] participants have varying levels of glucose control despite everyone receiving their glucose values in real time. Social cognitive theory suggests that simply providing CGM data, with or without alarms, will be insufficient to ensure that people with diabetes implement appropriate glucose management behaviors. Additionally, Pettus and Edelman write about the variation in behavioral responses to CGM data, describing a study of 222 participants who reported a wide range of insulin dosing, insulin timing, and carbohydrate consumption responses to the same scenarios of CGM-delivered glucose information.[13,14]

In Chapter 3, we demonstrated that the following behavioral constructs were adequately measured in the REPLACE-BG study: hypoglycemia avoidance behavior, hypoglycemia reaction behavior, and hypoglycemia prevention behavior. Hypoglycemia avoidance behavior represents behaviors that are performed with the intent of keeping glucose high in order to avoid any potential hypoglycemia. Hypoglycemia reaction behavior represents behaviors that a person may engage in once their glucose is already low in order to return to euglycemia. Hypoglycemia prevention behavior represents currently promoted glucose management behaviors that are performed to prevent hypoglycemia, but are not attached to keeping glucose levels high in order to avoid hypoglycemia. Since CGM is becoming a norm in diabetes management, it is of interest to understand which hypoglycemia behavior constructs are related to the occurrence of hypoglycemic events in a population of people with type 1 diabetes who all use CGM and insulin pumps to manage their glucose.

In this study, we use CGM data to classify the severity of hypoglycemic events in a population of people with well-controlled diabetes, and explore how the frequency and duration

of hypoglycemic events are associated with hypoglycemia avoidance, reaction, and prevention behavior constructs. Our classification of hypoglycemic event severity is based on previous thresholds for mild and moderate hypoglycemia.[9–11] We hypothesize that higher levels of hypoglycemia prevention behavior will be associated with a lower percent occurrence and shorter duration of moderate hypoglycemic events, and that participants who report higher levels of hypoglycemia avoidance behavior, compared to lower levels, will have a higher mean glucose and fewer total hypoglycemic events.

Methods

Sample

This analysis examined data from 216 participants who recorded ≥ 14 days of CGM data and completed the baseline and end of study surveys. We chose 14 days as a minimum amount for CGM data because glucose metrics from a 14-day sampling period of CGM data have been shown to be sufficient to categorize behavioral response patterns that correlate highly with glucose metrics from sampling periods of 30-days to 3 months.[15]

Study Design

This analysis used data from the Replace-BG Trial, which has been previously described.[11] Briefly, this trial was a 6-month, two-arm, randomized (2:1), controlled trial that compared glucose outcomes between participants who used CGM-only versus CGM with confirmatory BGM (fingerstick blood glucose meter). All participants used a Dexcom G4 Platinum CGM System (Dexcom, Inc., San Diego, CA) with an enhanced algorithm (Software 505), which measures glucose concentrations from interstitial fluid in the range of 40- 400 mg/dL every 5 minutes for up to 7 days.

This analysis does not distinguish participants by study group since the primary outcome paper reported no significant differences in glucose metrics between study groups or over time and because the presence or absence of adjunctive BGM is not hypothesized to impact glucose management outcomes.

Measures

Demographic and diabetes history information was collected via questionnaire at the initial screening visit. A1C was measured at a central laboratory (Northwest Lipid Research Laboratories, University of Washington, by using the Diabetes Control and Complications Trial standardized analyzer (Tosoh Bioscience, South San Francisco, CA)); A1C measurement at the 26-week time point of the trial was used in this analysis since it reflects the participants' glucose levels over the study period.

The hypoglycemia avoidance behavior, hypoglycemia reaction behavior, and hypoglycemia prevention behavior constructs explored in this analysis were measured at the 26-week visit through administration of the Hypoglycemia Fear Survey- Behavior subscale.[16] Each item was answered on a scale of 0-4, with greater values indicating greater likelihood of occurring; mean scores were generated for each item and each construct.

For each participant, we plotted the time trend for glucose readings over the duration of the study period and calculated the percent time and mean (SD) minutes/ day spent in euglycemia (70- 180 mg/dL), hyperglycemia (> 180 mg/dL), mild hypoglycemia (<70 mg/dL and >50 mg/dL), and moderate hypoglycemia ($\leq$ 50 mg/dL); mean (SD) glucose; and glucose coefficient of variation. For each instance that the glucose curve went below 70 mg/dL, we measured the duration until the glucose value returned to above 70 mg/dL, and we recorded the minimum glucose value during each "hypoglycemic event."

We created hypoglycemic event categories by stratifying total hypoglycemic events by the minimum glucose value reached during the event (mild events: 51-70 mg/dL, moderate events: ≤ 50 mg/dL).[9–11] These decision rules utilize the ADA definition for mild hypoglycemia and characterize moderate hypoglycemia using the ≤ 50 mg/dL cutpoint applied in the primary outcomes paper for the REPLACE-BG study. The following metrics were calculated for each hypoglycemic event category on the participant level: mean frequency of weekly mild or moderate events, percent of total weekly events that were mild or moderate, and mean duration of mild and moderate events.

Analysis

We reported the mean (SD) weekly frequencies of mild and moderate hypoglycemic events for standard demographic categories and performed ANOVA to test for differences across categories. We created high- and low- score categories for each hypoglycemia behavior construct using the median score of the respective construct's scale to divide the population into two categories. Then, we performed ANOVA to determine how glucose metrics vary between low and high categories of hypoglycemia avoidance behavior, hypoglycemia reaction behavior, and hypoglycemia prevention behavior constructs. We performed additional ANOVA to determine how the following vary between low and high categories of hypoglycemia behavior constructs: weekly frequency of total hypoglycemic events, percent occurrence of weekly hypoglycemic events that were moderate (of total hypoglycemic events), and weekly frequency and duration of mild and moderate hypoglycemic events. We reported mean (SD) for all variables. We considered p-values <0.05 to be statistically significant and p-values <0.1 to be borderline statistically significant.

We conducted univariable and multivariable linear regression to examine the association of the hypoglycemia behavior constructs with 1) duration of moderate hypoglycemic events and 2) percentage of moderate hypoglycemic events. Separate parsimonious multivariable linear regression models were built for each outcome, and both models included all three hypoglycemia behavior constructs in their continuous forms as predictors. Study site, age, and gender were included as covariates in both models to control for the multi-cohort nature of the population and multi-site nature of the study. Univariate associations were tested between each model outcome and BMI, glucose coefficient of variation and percent time in euglycemia--- variables with p-values <0.2 in univariable models were considered as covariates in multivariable models, where p-values <0.05 were considered statistically significant. SAS 9.4 was used for all analyses.

Results

A total of 216 participants were included in the analysis: 50% were female, 94% were white, 56% were over 40 years old, 56% had diabetes for more than 20 years, and 66% were overweight or obese (BMI > 25 kg/m^2) (Table 4.1). Sixty-five percent of participants reported never experiencing a severe hypoglycemic event, defined as needing help from another person to recover from low glucose, and the remaining participants reported not experiencing severe hypoglycemia in the past year. Seventy-four percent of participants reported never experiencing DKA, and the remaining participants reported not experiencing more than one DKA episode in the previous year.

Each participant recorded a mean (SD) of 162.2 (25.3) days of CGM data during the study period. All 216 participants experienced at least one mild hypoglycemic event during the study period, and 214 participants experienced at least one moderate hypoglycemic event during the study period. The mean frequency of weekly mild hypoglycemic events ranged from 4.3- 6.8

across demographic categories, and the mean frequency of weekly moderate hypoglycemic events ranged from 1.4- 2.2. Most differences between categories of the same demographic variables were small, but the largest differences occurred in age, A1C, and ethnicity. Participants ≤ 40 years recorded 6.5 mild and 2.2 moderate hypoglycemic events per week, compared to participants > 40 years recorded 6.0 mild and 1.6 moderate hypoglycemic events per week. People who were of non-White ethnicity recorded 6.3 mild and 1.9 moderate hypoglycemic events per week, compared to people of White ethnicity recording 4.3 mild and 1.4 moderate hypoglycemic events per week. Notably, people with A1C ≤ 7 % recorded 7.8 mild and 2.3 moderate hypoglycemic events per week, while people with A1C > 7% recorded 4.8 mild and 1.5 moderate hypoglycemic events per week (Table 4.1).

The mean (SD) score for hypoglycemia avoidance behavior was 1.2 (0.6), on a scale of 0- 4 (Table 4.2). The two items that had the highest mean scores--- 1.4 (0.8) and 1.6 (1.0)--- were "Eat large snacks at bedtime" and "If test blood glucose, run a little high to be on the safe side." The two items that had the lowest mean scores--- 0.7 (0.8) and 0.9 (1.0)--- were "Keep my sugar high when I will be alone for a while" and "Avoid being alone when my sugar is likely to be low." The mean (SD) score for hypoglycemia reaction behavior was 2.5 (0.8), and the mean (SD) score for hypoglycemia prevention behavior was 2.9 (0.8). The mean score for "Carry fast-acting sugar with me" was 3.5 (1.0).

Hypoglycemia avoidance behavior scores ranged from 0.0- 1.1 and 1.2- 3.2 in low and high categories, respectively (Table 4.3). Hypoglycemia reaction behavior scores ranged from 0.5- 2.4 and 2.5- 4.0 in low and high categories, respectively. Hypoglycemia prevention behavior scores ranged from 0.0- 2.9 and 3.0- 4.0 in low and high categories, respectively.

A1C, mean glucose, and minutes/ day in euglycemia varied significantly between categories of hypoglycemia avoidance behavior: A1C 6.9% vs. 7.2%, mean glucose 155.0 vs. 165.8 mg/dL, and minutes/ day in euglycemia 958.3 vs. 867.0, respectively in low vs. high categories (all p-values < 0.001) (Table 4.3). Neither minutes per day spent in mild or moderate hypoglycemia, nor glucose coefficient of variation varied between categories of any hypoglycemia behavior construct. Additionally, no aggregate glucose metrics varied significantly between low and high categories of hypoglycemia reaction behavior or hypoglycemia prevention behavior (Table 4.3).

The mean weekly frequencies of total and mild hypoglycemic events varied significantly between categories of hypoglycemia avoidance behavior: 8.8 vs. 7.5 total events/ week and 6.7 vs. 5.7 mild events/ week in low vs. high categories, respectively (all p-values < 0.05) (Table 4.4). For moderate hypoglycemic events, the percent of total events, frequency, and duration did not vary significantly by category of hypoglycemia avoidance behavior. In low vs. high categories of hypoglycemia reaction behavior, the weekly frequencies of total and mild hypoglycemic events were 8.5 vs. 7.8 and 6.6 vs. 6.0, respectively, but were not significantly different. In both categories of hypoglycemia reaction behavior, the weekly frequency of moderate hypoglycemic events was 1.9, and mean duration was 69 minutes, (Table 4.4).

In low vs. high categories of hypoglycemia prevention behavior, the mean (SD) weekly frequency of moderate hypoglycemic events was 2.1 (1.6) vs. 1.8 (1.4), respectively, and borderline significant ($p < 0.1$); the mean duration of moderate hypoglycemic events was 73.0 and 66.0 minutes, respectively, and significant ($p <0.05$); and the mean duration of mild hypoglycemic events was 29.8 minutes vs. 28.3 minutes, respectively, and borderline significant ($p< 0.1$) (Table 4.4).

In conducting the multiple linear regression analysis for the outcome "Duration of Moderate Hypoglycemic Events," we included the hypoglycemia avoidance, reaction, and prevention scales in their continuous forms and adjusted for study site, gender, and age. BMI did not have a significant univariate association with "Duration of Moderate Hypoglycemic Events" and was not tested in the multivariate model. Percent time in euglycemia had a significant univariate association with "Duration of Moderate Hypoglycemic Events," but was not significant in the multivariate model and was not retained in the final model. Glucose coefficient of variation had a significant association with the outcome in both univariate in multivariate models, and was retained in the final model. The final model included the hypoglycemia avoidance, reaction, and prevention behavior scales, study site, age, gender, and glucose coefficient of variation. The model included the 214 participants who experienced at least one moderate hypoglycemic event during the study period. In the final model (Table 4.5), higher scores of hypoglycemia prevention behavior were significantly associated with shorter duration of moderate hypoglycemic events (beta= -6.9, SE= 2.2, $p< 0.01$). Greater glucose coefficient of variation was significantly associated with longer duration of moderate hypoglycemic events (beta= 1.9, SE=0.3, $p< 0.0001$).

A similar process was used in conducting the multiple linear regression analysis for the outcome "Percent Occurrence of Moderate Hypoglycemic Events." BMI was not significantly associated with the outcome in univariate models, so was not included in the multivariate model. Percent time in euglycemia had a significant univariate association with the outcome, but was not significant in the multivariate model and was not retained in the final model. Glucose coefficient of variation had a significant association with the outcome in both univariate in multivariate models, and was retained in the final model. The final model (Table 4.5) included

the hypoglycemia avoidance, reaction, and prevention behavior scales, study site, age, gender, and glucose coefficient of variation. In the final model, higher scores of hypoglycemia prevention behavior were significantly associated with a lower percentage of moderate hypoglycemic events (beta= -2.2, SE= 0.7, p-value < 0.01), greater glucose coefficient of variation was associated with a higher percentage of moderate hypoglycemic events (beta= 1.0, SE= 0.1, p < 0.0001), and being female was significantly associated with a higher percentage of moderate hypoglycemic events (beta= 2.8, SE= 1.1, p <0.05).

Discussion

In this study of CGM-measured hypoglycemic events, we identified that hypoglycemic events were frequent for all T1D regardless of their A1C level, demographics, or level of hypoglycemic avoidance, reaction, and prevention behavior. However, the level of hypoglycemia prevention behavior was the main variable that differentiated the frequency and duration of moderate hypoglycemic events. Participants in the lower category for hypoglycemia prevention behavior experienced hypoglycemic events an average of 2.1 times per week, lasting an average duration of 73.0 minutes, compared to participants in the high score category experiencing an average 1.8 moderate hypoglycemic events per week that lasted 66.0 minutes.

We define moderate hypoglycemic events as having a minimum glucose value $\leq$ 50 mg/dL, which is both uncomfortable and dangerous to experience. Each hypoglycemic event requires a behavioral response to correct for hypoglycemia, and is accompanied by potentially dangerous low glucose symptoms. The higher percentage of moderate hypoglycemic events in participants in the lower category of hypoglycemia prevention behavior indicates that these participants do not respond to decreasing glucose levels as quickly as participants who are in the higher category of hypoglycemia prevention behavior, and mild hypoglycemic events are less

likely to be prevented from becoming moderate. The more frequent and longer duration moderate hypoglycemic events experienced by participants who engage in fewer hypoglycemia prevention behaviors put them at higher risk for problems associated with hypoglycemia, such as car crashes and disruptions in work or social events.

The percent occurrence of moderate hypoglycemic events ranged between 20.3% and 22.4% across all categories of hypoglycemia avoidance, reaction, and prevention behavior. It is important to notice that, across this population of participants with well-controlled diabetes (mean (SD) A1C of 7.0 (0.2)), about a fifth of all hypoglycemic events are severe. Since all participants received real-time CGM data and alarms when their glucose drops < 70 mg/dL, the likelihood of a mild hypoglycemic event becoming moderate depends on a person's likelihood of paying attention to their CGM values and alarms, and their preparation of having a carbohydrate source available.

In our multivariable analyses that assessed the association of hypoglycemia avoidance, reaction, and prevention behavior constructs with the outcomes 1) duration of moderate hypoglycemic events and 2) percentage of moderate hypoglycemic events, we found that hypoglycemia prevention behavior was the only hypoglycemia behavior construct that was significantly associated with the hypoglycemic event metrics.

Our final multivariate model that assessed the association of the duration of moderate hypoglycemic events with hypoglycemia prevention behavior indicated that for every 1-point increase in a participant's hypoglycemia prevention behavior score, the participant has a 7 minute decrease in the mean duration of their moderate hypoglycemic events ($p < 0.01$). Additionally, for every 4.2-unit decrease in a participant's glucose coefficient of variation, their mean duration of moderate hypoglycemic events decreases by 5 minutes ($p < 0.001$).

Our final multivariate model that assessed the association of the percent occurrence of moderate hypoglycemic events with hypoglycemia prevention behavior indicated that for every 1-point increase in a participant's hypoglycemia prevention behavior score, the participant has a 2% decrease in the percent occurrence of moderate hypoglycemic events ($p < 0.01$). Additionally, for every 1-unit decrease in a participant's glucose coefficient of variation, the participant has a 1% decrease in their percent occurrence of moderate hypoglycemic events ($p < 0.0001$). The model also indicated that females have a 2.8% higher percent occurrence of moderate hypoglycemic events compared to males, when all other conditions are held constant ($p < 0.05$).

These regression results indicate that participants who are more likely to engage in hypoglycemia prevention behaviors--- carrying fast-acting sugar in case of hypoglycemia, avoiding exercise if glucose is already low, and self-monitoring glucose levels--- have a significantly lower likelihood of mild hypoglycemic events becoming moderate. In the case that a hypoglycemic event is moderate, these participants are able to recover from hypoglycemia significantly faster than participants who are less likely to engage in hypoglycemia prevention behaviors.

Our findings in Table 4.1 show that females and males have the same mean weekly frequency moderate hypoglycemic events, and that males experience 0.4 more weekly mild hypoglycemic events than females. The finding in the multivariate model that females have a significantly higher percent occurrence of moderate hypoglycemic events than males (2.8% greater occurrence) may be a function of smaller denominator of total events (0.4 fewer total hypoglycemic events per week), which is not a material difference and does not suggest a greatly higher risk for moderate hypoglycemia when interpreted in context.

The significant increase in A1C and mean glucose between low and high categories of hypoglycemia avoidance behavior, and significant decrease in percent time spent in euglycemia, demonstrate how a person's entire glucose curve shifts upward as their likelihood for engaging in hypoglycemia avoidance behaviors increases. Oppositely, the glucose coefficient of variation does not vary across any hypoglycemia behavior construct. This illustrates a main challenge of glucose management, pointed out by Kovatchev,[17,18] which is the likely increased frequency of hypoglycemia upon lowering mean glucose due to the difficulty of decreasing the variation of glucose. The glucose coefficient of variation is determined largely by the activity of insulin and the absorption rate of carbohydrates into a person's blood--- two factors that are challenging to control, but may be improved through use of CGM as people can better understand the timeline in which their food, insulin, and physical activity impact their glucose.

The glucose coefficient of variation represents how widely a person's glucose values fluctuate around their mean glucose, and was positively and significantly associated with both duration and percentage of moderate hypoglycemic events in final models. These associations indicate that participants who have larger fluctuations in their glucose have a higher likelihood of mild hypoglycemic events becoming moderate, and take longer to return to euglycemia from moderate hypoglycemic events. This suggests that a greater coefficient of variation increases participants' risk for problems associated with hypoglycemia and is an indicator of poor glucose control.

The range of hypoglycemia behavior construct scores across the population confirms the variation in behavioral responses to CGM data recognized by Pettus et al.[14] In this study, hypoglycemia prevention behavior was able to predict exposure to moderate hypoglycemia, and higher hypoglycemia avoidance behavior scores were significantly related to increased glucose

levels. An ideal scale for evaluating the relationship between behaviors and glucose management would measure both hypoglycemia prevention behavior and hyperglycemia prevention behaviors. Measuring the behaviors that impact both sides of the euglycemic range would allow for the prediction of hypoglycemic and hyperglycemic event duration and frequency, glucose coefficient of variation, and combinations of behaviors that maximize time spent in euglycemia.

A key observation made in this study is the lack of variation in A1C across low and high score categories for hypoglycemia prevention behavior, but significantly longer duration and higher percentage of moderate hypoglycemic events in low vs. high hypoglycemia prevention behavior categories. Alternatively, A1C is significantly lower in low vs. high hypoglycemic avoidance behavior score categories, but there is no significant difference in occurrence of moderate hypoglycemic events. The discordant variation of A1C and moderate hypoglycemic events can be explained by the small amount of time spent in moderate hypoglycemia, which has a minute impact on average glucose levels and A1C. This highlights the importance of using CGM to measure glucose control, since any time in moderate hypoglycemia is physiologically dangerous and disruptive to a person's daily activities, but can be easily missed by an A1C test.

Also of interest is the lack of variation in mild and moderate hypoglycemic event frequency across categories of history of severe hypoglycemia--- a hypoglycemic event that required help from another individual to recover from--- and history of DKA. The participants in this study were chosen for having very good glucose control; 65% of participants reported having never experienced severe hypoglycemia and 74% reported not having experienced DKA within the past year. Regardless of participants reporting ever or never experiencing severe hypoglycemia, they had a mean of 1.9 moderate hypoglycemic events per week and 6.1 or 6.3 mild hypoglycemic events per week (respectively). The same frequencies applied to participants

who reported ever or never experiencing DKA. These uniform frequencies indicate that, in this population of well-controlled T1Ds, past experiences do not seem to impact the participants' current frequency of hypoglycemic events.

A limitation of our study is that the study population is not generalizable to the population of people with type 1 diabetes in America. A 2015 demographic description of the Type 1 Diabetes Exchange clinic registry,[19] from which the REPLACE-BG (RBG) population was recruited, reported an average A1C of 8.4% (7.0% in RBG), 83% white race (90% in RBG), and 34% reporting incomes greater than $100,000/ year (39% in RBG). Sixty percent of the Type 1 Diabetes Exchange population reported using an insulin pump, and 11% reported using a CGM, whereas the entire RBG population utilized insulin pumps and CGMs during the study period.

Our data indicate that all participants experience mild and moderate hypoglycemic events, regardless of A1C, demographics, or level of hypoglycemia avoidance, reaction, and prevention behavior. Our analysis shows that increased levels of hypoglycemia prevention behavior are associated with shorter durations of hypoglycemic events and a greater likelihood of preventing mild hypoglycemic events from becoming moderate. Our paper highlights the variation in behavioral responses to CGM data and illustrates the advantages of measuring glucose control with CGM versus A1C in order to accurately measure hypoglycemia. This paper utilizes CGM data in its continuous form to enhance the understanding of how hypoglycemic events relate to the hypoglycemia behavior constructs and suggests the importance of promoting hypoglycemia prevention behaviors to mitigate the risks of diabetes.

Table 4.1: Weekly frequency of mild and moderate hypoglycemic events by demographic categories (N=216)[a,b]

	N (%)	Mild hypoglycemic events	Moderate hypoglycemic events
Age, years			
≤ 40 years	96 (44)	6.5 (3.7)	2.2 (1.7)
> 40 years	120 (56)	6.0 (2.9)	1.6 (1.3)
BMI (kg/m2)			
≤25 kg/m2	73 (34)	6.8 (3.4)	2.0 (1.4)
>25 kg/m2	143 (66)	5.9 (3.2)	1.9 (1.6)
Gender			
Female	108 (50)	6.0 (3.2)	1.9 (1.4)
Male	108 (50)	6.4 (3.4)	1.9 (1.6)
A1C[*]			
≤ 7%	102 (47)	7.8 (3.6)	2.3 (1.7)
> 7%	114 (53)	4.8 (2.2)	1.5 (1.2)
Income			
<$50,000	23 (11)	5.8 (3.0)	1.7 (1.4)
$50,000- $100,000	55 (25)	6.5 (3.9)	2.0 (1.7)
>$100,000	84 (39)	6.4 (3.1)	1.9 (1.5)
Unknown/ Missing	54 (25)	5.9 (3.1)	1.8 (1.4)
Ethnicity			
White	203 (94)	4.3 (2.2)	1.4 (1.3)
Other/ Unknown	13 (6)	6.3 (3.3)	1.9 (1.5)
Duration of Diabetes			
≤ 20 years	96 (44)	6.1 (3.3)	1.7 (1.5)
>20 years	120 (56)	6.3 (3.3)	2.0 (1.5)
History of Severe Hypoglycemia			
Yes	76 (35)	6.1 (3.2)	1.9 (1.6)
No	140 (65)	6.3 (3.4)	1.9 (1.5)
History of DKA			
Yes	57 (26)	6.1 (3.5)	1.9 (1.5)
No	159 (74)	6.3 (3.2)	1.9 (1.5)

[a]Mild hypoglycemic events have a minimum value <70 mg/dL and >50 mg/dL. Moderate hypoglycemic events have a minimum value ≤50 mg/dL.
[b]Frequencies of hypoglycemic events are reported as mean (SD).
[*]A1C measured at 26-week visit (end of study).

Table 4.2: Hypoglycemia Behavior Constructs, Items, and Scores (n=216)[a]

Construct	Item Content	Item Score[b]	Construct Score[b]
Hypoglycemia Avoidance Behavior	Eat large snacks at bedtime	1.4 (0.8)	1.2 (0.6)
	Avoid being alone when my sugar is likely to be low	0.9 (1.0)	
	If test blood glucose, run a little high to be on the safe side	1.6 (1.0)	
	Keep my sugar high when I will be alone for a while	0.7 (0.8)	
	Keep my sugar high when I plan to be in a long meeting	1.2 (0.9)	
Hypoglycemia Reaction Behavior	Eat something as soon as I feel the first sign of low blood glucose	2.7 (1.0)	2.5 (0.8)
	Reduce my insulin when I think my sugar is low	2.2 (1.0)	
Hypoglycemia Prevention Behavior	Carry fast-acting sugar with me	3.5 (1.0)	2.9 (0.8)
	Avoid exercise when I think my sugar is low	2.8 (1.1)	
	Check my sugar often when I plan to be in a long meeting or party	2.4 (1.1)	

[a]All items are responded to in the context of "How likely are you to perform these behaviors?" with response options on a 0-4 scale. A response of 0 indicates "never" and 4 indicates "always."
[b]Scores reported as mean (SD).

Table 4.3: Glucose metrics across categories of Hypoglycemia Behavior Constructs (n=216)[a]

	Hypoglycemia Avoidance		Hypoglycemia Reaction		Hypoglycemia Prevention	
	Low Score Category	**High Score Category**	**Low Score Category**	**High Score Category**	**Low Score Category**	**High Score Category**
Score Range[b]	0.0- 1.1	1.2- 3.2	0.5- 2.4	2.5- 4.0	0.0- 2.9	3.0- 4.0
N (%)	105 (48.6)	111 (51.4)	87 (40.3)	129 (59.7)	85 (39.4)	131 (60.7)
A1C	**6.9 (0.6)**	**7.2 (0.7)**	7.0 (0.6)	7.0 (0.7)	7.0 (0.6)	7.0 (0.7)
Mean Glucose, mg/dL	**155.0 (18.9)**	**165.8 (24.1)**	157.1 (21.2)	162.9 (22.8)	161.1 (20.7)	160.1 (23.4)
Euglycemia, Minutes/day[c]	**958.3 (156.1)**	**867.0 (191.4)**	934.1 (178.7)	896.0 (180.9)	907.9 (170.1)	913.6 (187.7)
Mild Hypoglycemia, Minutes/ day[d]	54.1 (36.1)	52.0 (36.7)	55.6 (38.8)	51.4 (34.6)	51.8 (36.8)	53.9 (36.1)
Moderate Hypoglycemia, Minutes/day[e]	7.9 (7.0)	8.8 (9.9)	8.4 (8.4)	8.3 (8.8)	8.7 (10.2)	8.2 (7.4)
Glucose Coefficient of Variation	36.5 (4.4)	37.5 (4.9)	36.7 (5.2)	37.3 (4.3)	37.1 (5.2)	37.0 (4.3)

[a]All values reported as Mean (SD).
[b]Score categories are formed by dividing the population above and below the median score for the respective hypoglycemia-related behavior scale.
[c]Euglycemia includes glucose values 70- 180 mg/dL.
[d]Mild hypoglycemia includes glucose values <70 mg/dL and >50 mg/dL.
[e]Moderate hypoglycemia includes glucose values $\leq$50 mg/dL.
Bold values indicate ANOVA p-value <0.05 testing across median score categories within Hypoglycemia Behavior construct.

Table 4.4: Hypoglycemic event characteristics across categories of Hypoglycemia Behavior Constructs (n=216)[a]

	Hypoglycemia Avoidance		**Hypoglycemia Reaction**		**Hypoglycemia Prevention**	
	Low Score Category	**High Score Category**	**Low Score Category**	**High Score Category**	**Low Score Category**	**High Score Category**
Score Range	0.0- 1.1	1.2- 3.2	0.5- 2.4	2.5- 4.0	0.0- 2.9	3.0- 4.0
N (%)	105 (48.6)	111 (51.4)	87 (40.3)	129 (59.7)	85 (39.4)	131 (60.7)
Total Hypoglycemic Events/ Week	**8.8 (4.8)**	**7.5 (4.1)**	8.5 (4.9)	7.8 (4.2)	8.4 (4.4)	7.9 (4.6)
% Moderate Hypoglycemic Events[b]	20.8 (9.0)	21.1 (9.6)	20.3 (8.2)	21.5 (9.9)	***22.4 (9.7)***	***20.1 (8.9)***
Mild Hypoglycemic Events[c]						
Events/ Week	**6.7 (3.5)**	**5.7 (3.0)**	6.6 (3.7)	6.0 (3.0)	6.2 (3.1)	6.2 (3.5)
Event Duration, minutes	28.7 (6.5)	29.0 (6.6)	28.6 (5.8)	29.0 (7.0)	***29.8 (7.0)***	***28.3 (6.1)***
Moderate Hypoglycemic Events[d]						
Events/ Week	2.0 (1.5)	1.8 (1.5)	1.9 (1.5)	1.9 (1.5)	***2.1 (1.6)***	***1.8 (1.4)***
Event Duration, minutes	67.8 (21.6)	69.7 (26.2)	68.9 (21.2)	68.7 (25.8)	**73.0 (24.7)**	**66.0 (23.2)**

[a]All values reported as Mean (SD).
[b]% of total events accounted for by moderate events.
[c]Mild hypoglycemic events have a minimum value <70 mg/dL and >50 mg/dL.
[d]Moderate hypoglycemic events have a minimum value ≤50 mg/dL.
Bold values indicate ANOVA p-value <0.05, ***Italicized bold*** values indicate ANOVA p-value <0.1, testing across median score categories within Hypoglycemia Behavior construct.

Table 4.5: Regression results for the associations of Hypoglycemia Behavior Constructs with duration (n=214) and percent occurrence (n=216) of moderate hypoglycemic events[a]

Outcome: Duration of Moderate Hypoglycemic Events			
	B	**SE**	**p-value**
Hypoglycemia Avoidance Behavior	2.5	2.5	0.3
Hypoglycemia Reaction Behavior	1.5	2.0	0.5
Hypoglycemia Prevention Behavior	-6.9	2.2	<0.01
Glucose Coefficient of Variation	1.9	0.3	<0.0001
Age, 5 years	-1.05	0.55	0.06
Gender	-2.1	3.2	0.5
Study Site	-0.2	0.3	0.5
Outcome: Percent Occurrence of Moderate Hypoglycemic Events			
Hypoglycemia Avoidance Behavior	-0.4	0.9	0.6
Hypoglycemia Reaction Behavior	0.5	0.7	0.4
Hypoglycemia Prevention Behavior	-2.2	0.7	<0.01
Glucose Coefficient of Variation	1.0	0.1	<0.0001
Age, 5 years	-0.35	0.2	0.06
Gender	2.8	1.1	<0.05
Study Site	-0.04	0.1	0.7

[a]Model for outcome "Duration of moderate hypoglycemic events" includes the 214 participants who experienced at least 1 moderate event during the study period.

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CHAPTER 5:

THE FREQUENCY AND DURATION OF SEVERE HYPERGLYCEMIC EVENTS VARIES BY A1C

Specific Aim: Develop categories of severity for hyperglycemic events and describe how time in different categories is related to A1C levels.

Hypothesis: *Participants at higher levels of A1C will experience more frequent hyperglycemic events and a higher percent of total hyperglycemic events that are severe.*

Introduction

Continuous glucose monitoring (CGM) is becoming a norm for managing type 1 diabetes (T1D)[1–3] and has been shown to reduce A1C in several randomized controlled trials.[4,5] CGM is a useful diabetes management tool because it provides real-time glucose levels and alerts for hyper- and hypoglycemia to people with T1D. CGM records a datastream that can be analyzed in its continuous form to describe events in glucose management, like individual hyperglycemic events, which are typically measured in aggregate form as the percent of time a person's glucose is above a set glucose threshold.

The current standard measure of blood glucose control for clinical decisions is the hemoglobin A1C, which measures average glucose levels over the previous three months.[6,7] The ADA target for A1C in people with T1D is below 7%, preferably around 6.5%,[8] and diabetes complications are more likely in people who maintain higher A1Cs.[9–11] The American Diabetes Association (ADA) recommends that people with T1D maintain their blood glucose levels between 70 and 180 mg/dL, called euglycemia,[8] and defines glucose levels >180 mg/dL as moderate hyperglycemia and glucose levels >250 mg/dL as severe hyperglycemia. There are both microvascular and macrovascular complications that are the consequences of too much time

spent in hyperglycemia,[6,12] and these are manifested as retinopathy, neuropathy, nephropathy, coronary artery disease, and stroke.[7,9,13–15]

While A1C does provide a good monitor of hyperglycemic exposure over the past three months, it does not provide feedback that is proximal to when the individual needs to make moment-to-moment management decisions or describe patterns in glucose levels that can be used to improve their glucose management behaviors--- either through self-reflection or through discussion with a health care provider. Thus, compared to CGM, A1C is not an optimal decision support tool for people with T1D.

CGM data from the REPLACE-BG trial[16] are publicly available and provide a detailed record of glucose levels over a period of 6 months for over 200 people with T1D. These data provide the opportunity to explore hyperglycemic events among T1D who are at four different levels of good blood glucose control. For each of these groups, we explore how different measures that describe these hyperglycemic excursions (i.e. the frequency of excursions, the maximum glucose level reached, and the time spent in hyperglycemia) are related to improved A1C levels. We hypothesize that we will be able to identify a metric that is the most powerful predictor of A1C levels so that in future studies we can identify glucose management practices that minimize exposure on this metric.

Methods

Sample

This analysis examined data from 216 participants who recorded $\geq$ 14 days of CGM data and completed the baseline and end of study surveys. We chose 14 days as a minimum amount for CGM data because glucose metrics from a 14-day sampling period of CGM data have been

shown to capture period prevalence of habitual glucose management and to correlate highly with glucose metrics from sampling periods of 30-days to 3 months.[17]

Study Design

This analysis used data from the REPLACE-BG trial[16] which has been previously described in the primary outcomes paper and in Chapters 2, 3, and 4 of this dissertation. Briefly, this trial was a 6-month trial in which all participants used a Dexcom G4 Platinum CGM System (Dexcom, Inc., San Diego, CA) with an enhanced algorithm (Software 505), which measures glucose concentrations from interstitial fluid in the range of 40- 400 mg/dL every 5 minutes. The trial was conducted at 14 endocrinology practices in the U.S. that are members of the Type 1 Diabetes Exchange Network.

Study inclusion and exclusion criteria are described in Chapter 4. Of specific relevance is that potential participants were excluded based on the occurrence of any severe hypoglycemic event, an event in which the person required assistance from another person to treat their low glucose levels, or diabetic ketoacidosis within the past year. The study randomized 226 participants between May 2015 and March 2016.

Measures

Demographic and diabetes history information was collected via questionnaire at the initial screening visit. A1C was measured at a central laboratory (Northwest Lipid Research Laboratories, University of Washington, by using the Diabetes Control and Complications Trial standardized analyzer (Tosoh Bioscience, South San Francisco, CA)); A1C measurement at the 26-week time point of the trial was used in this analysis since it reflects the participants' glucose levels over the study period.

We plotted all available glucose readings for each participant's CGM data and calculated the percent time in hyperglycemia (> 180 mg/dL) and euglycemia (70- 180 mg/dL), as well as mean (SD) glucose level and glucose coefficient of variation. For each hyperglycemic event, we measured the duration that the glucose level was above 180 mg/dL (a single hyperglycemic event), and we recorded the maximum glucose value during the event.

To categorize the severity of hyperglycemic events, we utilize the ADA definition of moderate hyperglycemia (180 to < 250 mg/dL) and severe hyperglycemia ($\geq$ 250 mg/dL),[8] in conjunction with their recommendation that meal-related hyperglycemic events should not last more than 2 hours. We divide the duration of events into three time-periods (5 -29.9 minutes, 30-119.9 minutes, and $\geq$ 2 hours) and binarize whether the maximum glucose level was beyond the 250 mg/dL threshold for severe hyperglycemia. Thus, we created the following 4 categories of hyperglycemic events: Category 1 = duration of less than 30 minutes; Category 2= duration of 30- 119.9 minutes; Category 3= duration $\geq$ 2 hours, maximum glucose value < 250 mg/dL; Category 4= duration $\geq$ 2 hours, maximum glucose value $\geq$ 250 mg/dL. We analyze all available CGM data in weekly increments and report the mean (SD) for the following metrics: total weekly events, percent of total hyperglycemic events accounted for by each severity category, and duration and maximum value of events by severity category.

Analysis

We reported the frequency and percent of total events for all hyperglycemic events recorded during the study period, by severity category. We performed ANOVA to determine how weekly frequency of total hyperglycemic events and percent occurrence of hyperglycemic events of each severity category varied within standard demographic categories. Descriptive

statistics were generated as means with standard deviations for continuous variables, and frequencies with percentages for categorical variables.

We categorized participants into quartiles of A1C measured at the 26-week time-point and performed ANOVA to determine how aggregate glucose metrics, mean weekly frequency of total events, and percent occurrence of events in each severity category varies across A1C quartiles. For each of these variables, we also performed linear regression with 26-week A1C to test for linearity.

We performed an additional ANOVA to determine how metrics specific to Cat 4 events--- total weekly events, duration, maximum glucose value, and percent of all time in hyperglycemia spent in Cat 4 events--- vary across A1C quartiles. In order to quantify and test for significant differences between individual A1C quartiles, we performed Bonferroni tests of differences.

We conducted univariable and multivariable linear regression to examine the association of A1C with 1) *percent occurrence of events in each severity category* and 2) *percent of all time in hyperglycemia spent in Category 4 events*. A1C was the outcome in both models, and separate parsimonious multivariable linear regression models were built for each primary predictor variable. Both models included study site, age, and gender as covariates to control for the multi-cohort nature of the population and multi-site nature of the study. In our first model (predictor: percent occurrence of events in each severity category), we included the percent occurrences of all hyperglycemic event categories in the initial model and used a data reduction approach to include the event categories that best predicted A1C. BMI, glucose coefficient of variation, and total weekly hyperglycemic events were tested as covariates based on their univariate association with the model outcome. Variables with p-values <0.2 in univariable models were considered as

covariates in multivariable models, where p-values <0.05 were considered statistically significant. SAS 9.4 was used for all analyses.

Results

A total of 101,020 hyperglycemic events occurred during the study period, over all participants. These events included many instances of each of the severity categories: 24% were Cat 1, 33% were Cat 2, 17% were Cat 3, and 26% were Cat 4 (Table 5.1).

A total of 216 participants were included in the analysis: 50% were female, 94% were white, 56% were over 40 years old, 56% had diabetes for more than 20 years, and 66% were overweight or obese (BMI > 25 kg/m^2) (Table 5.2). Seventy-four percent of participants reported never experiencing DKA, and the remaining participants reported not experiencing more than one DKA episode in the previous year.

Each participant recorded a mean (SD) of 162.2 (25.3) days of CGM data during the study period. The mean frequency of weekly hyperglycemic events ranged from 16.2- 19.4 across demographic categories. The mean percent of total hyperglycemic events accounted for by each severity category ranged from 22.3- 26.7 for Cat1 events, 29.9- 36.9 for Cat2 events, 15.4- 17.7 for Cat3 events, and 19.3- 31.8 for Cat 4 events (Table 5.2). Most differences between categories of the same demographic variables were small, but participants with an A1C $\leq$ 7% vs. >7% experienced 16.2 (4.2) vs. 19.4 (3.9) mean (SD) weekly hyperglycemic events, of which 26.7% (5.3%) vs. 22.3% (3.9%) were Cat1, 36.9% (7.1%) vs. 29.9% (6.1%) were Cat2, and 19.3% (8.5%) vs. 31.8% (9.8%) were Cat4--- all differing significantly between A1C categories. Participants $\leq$ 40 vs. > 40 years old experienced 23.6% (5.1%) vs. 25.0% (5.0%) Cat 1 events, 15.4% (3.7%) vs. 17.7% (5.1%) Cat 3 events, and 28.0% (11.7%) vs. 24.2% (10.3%) Cat 4 events--- all differing significantly between age categories (Table 5.2). Participants who had ever

vs. never experienced DKA experienced a significantly different amount of cat 4 events--- 28.4% (10.6%) vs. 25.0% (11.1%) respectively.

Participants were categorized based on 26-week A1C quartiles. Mean glucose and percent of time spent in euglycemia, hyperglycemia (>180 mg/dL), and severe hyperglycemia (>250 mg/dL) had significant trends across A1C quartiles. Mean glucose and percent time in hyperglycemia (>180 mg/dL) increased in each higher A1C quartile, percent time in euglycemia decreased in each higher A1C quartile, and glucose coefficient of variation did not vary across A1C quartiles. Participants in each higher quartile spent 333.2 (169.9), 426.1 (140.8), 552.3 (149.0), and 631.6 (183.8) minutes in hyperglycemia respectively (p-value for linearity <0.0001) (Table 5.3).

The mean frequency of weekly events per participant varied significantly across A1C quartiles ($p < 0.0001$ for ANOVA and linearity tests) (Table 5.3). Even in the lowest A1C quartile, there were an average of 15 hyperglycemic events every week during the study. While the frequency of events was significantly higher for those in the upper quartile of A1C compared to the lowest quartile, these participants experienced an average of only 3 additional events per week. The mean frequency of weekly events increased across A1C quartiles 1, 2, and 3 (15.0, 18.1, 20.7 events/ week, respectively), but decreased to 18.0 events / week in A1C Quartile 4 (Table 5.3).

The percent occurrence of Cat 1 and Cat 2 events decreases significantly in higher A1C quartiles, individually and combined (Cat1 and Cat 2 events combined are "non-severe events," p-values for linearity <0.0001). Cat 3 events did not vary significantly across A1C quartiles and Cat 4 events increase significantly in higher A1C quartiles (p-value for linearity < 0.0001) (Table 5.3). The percent of non-severe events (cumulative percent of Cat 1 and Cat 2 events) was

66.2% (9.7%), 60.0% (7.8%), 54.7% (7.7%), and 49.1% (7.6%) in respective increasing A1C quartiles. The composition of events in the lowest A1C quartile was: 27.1± 5.6 % Cat1, 39.1 ± 6.8% Cat 2, 16.5 ± 5.1% Cat 3, and 17.6 ± 7.8% Cat 4 (Table 5.3). Comparatively, the composition of events in the highest A1C quartile was: 21.8 ± 3.7% Cat 1, 27.3 ± 5.9% Cat 2, 16.4 ± 4.7% Cat 3, and 34.5 ± 10.5% Cat 4 (Table 5.3).

Table 5.4 presents the data for Cat 4 events, including p-values from ANOVA and indicates that participants in the lowest quartile of A1C had an average of 2.8 ±1.5 Cat 4 events/ week, the mean event duration was 294.1± 66.7 minutes (~5 hours) and the maximum glucose level during this period was an average of 290.3±9.8 mg/dL. Those in the highest quartile of A1C had more than twice as many Cat 4 events /week (6.1±1.9, Bonferroni $p < 0.0001$) as A1C Quartile 1, the mean duration was 46% longer with a lot more variation in length (428.3 ± 111.9 minutes, ~7 hours, Bonferroni $p < 0.0001$), and the maximum glucose reached was an average of 6% higher (Bonferroni $p < 0.0001$). A1C Quartile 2 was differentiated from A1C Quartile 1 on both the number of events /week (4.3± 2.1, Bonferroni $p < 0.001$) and their average duration (333.9± 86.0 minutes, ~5.5 hours, Bonferroni $p = 0.07$), though not on the average maximum glucose attained (Bonferroni $p = 0.44$). A1C Quartile 3 differed from A1C Quartile 2 in the number of events per week (6.0±1.8, Bonferroni $p < 0.0001$) and average maximum glucose value attained (Bonferroni $p < 0.05$), but not in the average duration (Bonferroni $p = 1.0$). A1C Quartile 4 did not differ from A1C Quartile 3 in the number of events per week ($p = 1.0$), but the average duration of event was 33% longer (Bonferroni $p < 0.0001$) and maximum glucose attained was 2% higher (Bonferroni $p = 0.11$) in A1C Quartile 4. Additionally, the percent of all hyperglycemic minutes accounted for by Cat 4 events increased significantly across A1C

quartiles: 43%, 52%, 62%, and 70% respectively. Only one participant did not experience a Cat 4 event during the study period.

In conducting the multiple linear regression analysis for the outcome A1C and the primary predictor "*percent occurrence of events in each severity category*," we found the percent occurrence of non-severe events (cumulative Cat 1 and Cat 2 events) to be significantly associated with A1C. Glucose coefficient of variation had a non-significant univariate association with A1C and was not tested in the multivariate model. BMI and total weekly hyperglycemic events had significant associations with A1C in both univariate in multivariate models, and were both retained in the final model. The final model included percent occurrence of non-severe hyperglycemic events, total weekly hyperglycemic events, BMI, age, gender, and study site. In the final model (Table 5.5), percent of non-severe events was significantly, inversely associated with A1C (beta= -0.04, SE =0.004, $p < 0.0001$). Total weekly events was significantly, positively associated with A1C (beta =0.02, SE =0.01, $p < 0.05$).

A similar process was used in conducting the multiple linear regression to evaluate the association of "*percent of all time in hyperglycemia spent in Cat 4 events"* and A1C. The above-described univariate association screening process informed the inclusion of BMI and total weekly events, but not glucose coefficient of variation, in the multivariate models. The final model adjusted for total weekly hyperglycemic events, BMI, age, gender, and study site. In the final model (Table 5.5), "*percent of all time in hyperglycemia spent in Cat 4 events"* was significantly, positively associated with A1C (beta= 0.03, SE=0.002, $p<0.0001$). Total weekly events was positively, but non-significantly associated with A1C (beta= 0.01, SE=0.009, p= 0.2). Age was significantly, positively associated with A1C (beta= 0.008, SE=0.003, $p< 0.05$).

Discussion

In this study of hyperglycemic events, we identified that hyperglycemic events were frequent for all T1D regardless of their A1C level. However, experiencing higher percentages of non- severe events (Cat 1 and Cat 2) was significantly associated with lower A1C, and a greater percent of time spent in hyperglycemia accounted for by Cat 4 events was significantly associated with increased A1C.

Participants in the highest A1C quartiles spend 2.5 times more time in hyperglycemia than participants in the lowest A1C quartiles (10.6 hours vs. 4.3 hours). The increase in daily minutes in hyperglycemia across increasing A1C quartiles, in conjunction with the increasing percent of all minutes in hyperglycemia accounted for by Cat 4 events, highlights the large amount of time that participants in higher A1C quartiles spend in Cat 4 events. Alternatively, participants in A1C quartiles 1 and 2 experience significantly more non-severe hyperglycemic events than participants in higher A1C quartiles.

The average duration of Cat 4 events differentiated individuals in different quartiles of A1C. Those in excellent control (A1C <6.5%) experienced category 4 events an average of 2.8 times per week, with each event lasting just under 5 hours. Those with an A1C range of 6.5-7.1% experienced such events 4.3 times per week, with each event lasting about 5.5 hours. Those with an A1C range of 7.2- 7.4% experienced such events an average of 6 times/ week, with each event lasting an average of 5.7 hours; and those with an A1C range of 7.5- 10.2% experienced such events an average of 6.1 times per week, with each event lasting 7.1 hours (33% longer than the previous A1C group). For each of the A1C groups the average maximum glucose reached during category 4 events was between 294 and 308 mg/dL.

Cat 4 events are the most severe as they have both long duration (>2 hours) and maximum glucose values ≥ 250 mg/dL. The mean duration of Cat 4 events in A1C Quartile 4 is more than 1 hour longer than the mean duration of the A1C Quartiles 2 and 3, and more than 2 hours longer than that of A1C Quartile 1. The mean event duration in A1C Quartile 4 is 7 hours, which accounts for more than 25% of a day, and is a significant amount of time for glucose levels to remain in hyperglycemia, especially when events of this type are occurring nearly daily (6.1 times/ week).

Participants in the lowest A1C quartile experience the fewest hyperglycemic events of any type, including Cat 4 events. While A1C Quartile 1 participants do experience some Cat 4 events, they are the shortest in duration and lowest in maximum value of all the A1C quartiles. Participants in A1C Quartile 2 experience fewer overall events and Cat 4 events than A1C Quartile 3 participants. However, the Cat 4 events that A1C Quartile 2 participants do experience are similar in duration to those of A1C Quartile 3 participants, and only slightly lower in maximum glucose value attained. This indicates that the glucose management behaviors that lead to Cat 4 events occur less frequently in A1C Quartile 2 participants, but that the glucose management behaviors that occur to manage a Cat 4 event once it has occurred are similar between A1C Quartile 2 and 3 participants.

Oppositely, participants in A1C Quartiles 3 and 4 experience the same weekly number of category 4 events, but the duration of category 4 events is significantly longer in A1C Quartile 4 participants. In fact, A1C Quartile 3 participants experience more total hyperglycemic events than A1C Quartile 4 participants, but are able to manage their glucose to experience a smaller percentage of category 4 excursions than A1C Quartile 4 participants. This indicates that the glucose management behaviors that lead to severe hyperglycemic events (Cat 3 and 4) occur at a

similar frequency in A1C Quartile 3 and 4 participants, but that the glucose management behaviors that occur once the event has begun are different between A1C Quartile 3 and 4 participants.

Key diabetes management behaviors are described by the ADA as insulin dosing, food choices, and physical activity.[8] A combination of food and insulin dosing decisions tend to precede hyperglycemic events--- determining frequency of events, while insulin dosing and physical activity are behavioral tools for lowering glucose back to euglycemia--- determining duration and maximum value of events. In this population of people with Type 1 Diabetes and in other recent studies using CGM in a T1D population,[4,5] all participants received their CGM-recorded glucose values in real time, yet they had varying levels of glucose control. This suggests that information alone does not drive glucose control and suggests the importance of understanding how diabetes management behaviors differ across A1C quartiles.

Our multivariate model that assessed the association of A1C with percent occurrence of non- severe hyperglycemic events indicated that for each 6.3% increase in occurrence of non-severe events, A1C value decreased by 0.25%. Additionally, for every 12.5 additional hyperglycemic events per week, A1C value increased by 0.25%. These results indicate that participants who are able to manage their hyperglycemic events to be non-severe have lower A1Cs, which is likely due to proactive glucose management behaviors--- like making food and insulin dosing decisions that allow for glucose to return back to euglycemia within two hours, as opposed to making an less effective food and insulin dosing decision that leads to prolonged hyperglycemia (cat 3 and cat 4 events).

Our finding that participants in A1C quartiles 3 and 4 have the same number of Cat 4 events, but are distinguished by event duration, suggests the potential for moving between A1C

quartiles solely through improved management of hyperglycemic events. Our final multivariate model that assessed the association of A1C with *percent time in hyperglycemia accounted for by Cat 4 events* indicated that for each 8.5% increase in *percent time in hyperglycemia accounted for by Cat 4 events*, A1C value increased by 0.25%. Since *percent time in hyperglycemia accounted for by Cat 4 events* reflects both the frequency and duration of cat 4 events, this finding highlights that both preventing and managing the duration of these events have an impact on A1C. Of note, participants' insulin administration patterns during hyperglycemic events reflect a participant's attentiveness to out-of-range glucose levels and are likely to impact duration of events, and insulin bolusing is a behavior that is hypothesized to vary across A1C quartiles. This points to the importance of understanding how diabetes management behaviors vary across A1C quartiles, especially in respect to glucose lowering behaviors.

Also of interest is the lack of variation across A1C quartiles for history of severe hypoglycemia, history of DKA, and glucose coefficient of variation. The consistent values of glucose coefficient of variation across A1C quartiles indicates that glucose coefficient of variation does not vary with a person's average glucose as measured by A1C. The participants in this study were chosen for having very good glucose control; 74% and 65% of participants reported having never experienced DKA or severe hypoglycemia (respectively). Among participants who reported past DKA or severe hypoglycemia, the uniform distribution across A1C quartiles suggests that these past experiences do not impact the participants' current A1C values. However, we do see that participants who have a history of DKA have a significantly higher occurrence of Cat 4 events than participants who have never experienced DKA, which suggests that these participants typically experience a higher severity of hyperglycemic events.

A limitation of our study is that the RBG population is not generalizable to the population of people with type 1 diabetes in America. A 2015 demographic description of the Type 1 Diabetes Exchange clinic registry,[1] from which RBG recruited, reported an average A1C of 8.4% (7.0% in RBG), 83% white race (90% in RBG), and 34% reporting incomes greater than $100,000/ year (39% in RBG). Sixty percent of the Type 1 Diabetes Exchange population reported using an insulin pump, and 11% reported using a CGM, whereas the entire RBG population utilized insulin pumps and CGMs during the study period.

A takeaway message for T1Ds and their health care providers is that it T1D in good glucose control experience hyperglycemia, and even severe hyperglycemic events, but that the shorter duration hyperglycemic events are associated with lower levels of A1C. This analysis suggests a glucose management goal of minimizing the duration of most hyperglycemic events to less than two hours. T1D can use CGM to optimize their glucose management by paying attention to hyperglycemia alarms, and using these alarms as a cue to action for assessing if an appropriate amount of fast-acting insulin is on board to return to euglycemia. CGM can be used as a self-reflection tool by T1Ds and a point of discussion with health care providers by reading through the past day's or week's CGM trace for hyperglycemic events, assessing the severity and duration of events, and planning for behavioral patterns that can mitigate the severity and duration of hyperglycemic events.

Our data indicate that regardless of A1C level, all participants spend time in hyperglycemia and most experience severe hyperglycemic events. Our analysis shows that at higher levels of A1C, participants have longer continuous durations of hyperglycemic exposure, which is a key risk factor for developing diabetes-related complications. Our analysis also indicates that experiencing mostly non- severe hyperglycemic events is associated with improved

A1C. This paper utilizes CGM data in its continuous form to enhance the understanding of how hyperglycemic events relate to A1C and suggests the importance of promoting glucose lowering behaviors in optimizing diabetes management.

Table 5.1: Description and Frequency of Hyperglycemic Event Severity Categories for Events Measured over Duration of Study, for All Participants (n=101, 020)

Category	Definition	Frequency	% of Total Events
Cat 1	Duration <30 minutes Any maximum glucose value	24,268	24%
Cat 2	Duration ≥30 minutes, < 2 hours Any maximum glucose value	33,304	33%
Cat 3	Duration ≥2 hours Maximum glucose value <250 mg/dL	16,804	17%
Cat 4	Duration ≥2 hours Maximum glucose value ≥250 mg/dL	26,644	26%
Total	-----	101,020	100%

Table 5.2: Weekly frequency of hyperglycemic events and percent composition of event severity by demographic categories (N=216)

			Percent of Total Hyperglycemic Events Accounted for by Severity Category[b]			
	N (%)	Weekly Events[a]	Category 1	Category 2	Category 3	Category 4
Age, years						
≤ 40 years	96 (44)	17.7 (4.4)	**23.6 (5.1)**	33.0 (7.9)	**15.4 (3.7)**	**28.0 (11.7)**
> 40 years	120 (56)	18.1 (4.4)	**25.0 (5.0)**	33.3 (7.1)	**17.7 (5.1)**	**24.2 (10.3)**
BMI (kg/m2)						
≤25 kg/m2	73 (34)	17.3 (5.2)	25.2 (5.3)	**34.7 (7.7)**	16.8 (4.5)	**23.6 (10.8)**
>25 kg/m2	143 (66)	18.2 (3.9)	23.9 (5.0)	**32.4 (7.2)**	16.6 (4.8)	**27.1 (11.1)**
Gender						
Female	108 (50)	18.5 (4.2)	23.9 (5.0)	33.3 (7.9)	**15.7 (4.3)**	24.5 (11.1)
Male	108 (50)	17.4 (4.2)	24.8 (5.1)	33.1 (7.0)	**17.6 (4.9)**	27.3 (10.9)
A1C						
≤ 7%	102 (47)	**16.2 (4.2)**	**26.7 (5.3)**	**36.9 (7.1)**	17.3 (4.9)	**19.3 (8.5)**
> 7%	114 (53)	**19.4 (3.9)**	**22.3 (3.9)**	**29.9 (6.1)**	16.1 (4.4)	**31.8 (9.8)**
Income						
<$50,000	23 (11)	18.2 (3.2)	24.3 (5.6)	32.6 (8.5)	**17.2 (4.6)**	25.9 (11.3)
$50,000- $100,000	55 (25)	17.8 (5.0)	24.7 (5.9)	34.0 (7.2)	**16.4 (4.7)**	25.4 (10.0)
>$100,000	84 (39)	17.8 (4.2)	24.8 (4.9)	33.1 (6.9)	**17.8 (4.3)**	24.4 (10.8)
Unknown/ Missing	54 (25)	18.2 (4.4)	23.3 (4.2)	32.8 (8.1)	**15.0 (4.8)**	28.8 (12.1)
Ethnicity						
White	203 (94)	17.9 (4.4)	24.4 (5.1)	34.3 (6.9)	18.2 (4.1)	26.1 (11.2)
Other/ Unknown	13 (6)	18.8 (3.6)	24.0 (5.1)	33.1 (7.5)	16.6 (4.7)	23.6 (9.7)
Duration of Diabetes						
≤ 20 years	96 (44)	17.8 (4.6)	24.7 (4.9)	33.7 (7.0)	16.5 (4.7)	25.4 (10.5)
>20 years	120 (56)	18.0 (4.2)	24.1 (5.2)	32.8 (7.8)	16.8 (4.7)	26.3 (11.6)
History of Severe Hypoglycemia[c]						
Yes	76 (35)	17.5 (4.1)	23.6 (5.1)	33.3 (7.5)	16.4 (4.8)	27.0 (10.9)
No	140 (65)	18.6 (4.8)	24.8 (5.1)	33.1 (7.5)	16.8 (4.6)	25.3 (11.2)
History of Diabetic Ketoacidosis[3]						
Yes	57 (26)	18.1 (4.3)	23.8 (5.3	32.3 (7.9)	16.0 (5.3)	**28.4 (10.6)**
No	159 (74)	17.8 (4.4)	24.5 (5.0)	33.5 (7.3)	16.9 (4.4)	**25.0 (11.1)**

[a]Weekly frequency of hyperglycemic events is reported as mean (SD).
[b]Percent of total hyperglycemic events accounted for by respective severity category, reported as mean (SD).
[c]History of DKA and Severe Hypoglycemia are reported as *Never* or as *Last episode occurring >6 and >12 months ago* (respectively), based on exclusion criteria.
Bold values indicate $p < 0.05$ for ANOVA testing across categories within demographic variables.

Table 5.3: Characteristics of Hyperglycemic Events by A1C Quartile Membership (N=216)[a,b]

	A1C Quartiles				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-value[e]**
N (%)	53 (24.5)	61 (28.2)	49 (22.7)	53 (24.5)	----
A1C Range, %	5.2-6.5	6.6- 7.1	7.2- 7.4	7.5- 10.2	----
Weekly Events	15.0 (4.3)	18.1 (4.0)	20.7 (3.9)	18.0 (3.5)	< 0.0001
Daily Minutes in Hyperglycemia	333.2 (169.9)	426.1 (140.8)	522.3 (149.0)	631.6 (183.8)	< 0.0001
Percent Cat 1[c]	27.1 (5.6)	25.6 (4.7)	22.5 (4.2)	21.8 (3.7)	< 0.0001
Percent Cat 2[c]	39.1 (6.8)	34.0 (6.2)	32.1 (5.8)	27.3 (5.9)	< 0.0001
Percent Non-Severe Events[c,d]	66.2 (9.7)	60.0 (7.8)	54.7 (7.7)	49.1 (7.6)	< 0.0001
Percent Cat 3[c]	16.5 (5.1)	17.7 (4.5)	15.8 (4.4)	16.4 (4.7)	0.07
Percent Cat 4[c]	17.6 (7.8)	22.6 (8.9)	29.5 (9.0)	34.5 (10.5)	< 0.0001

[a]All statistics reported as mean (SD).
[b]A1C quartiles calculated from 26-week A1C.
[c]Percent of total hyperglycemic events accounted for by respective severity category.
[d]Cumulative Cat1 and Cat2 events are defined as "Non-Severe events."
[e]p-value is calculated from test for linearity with 26-week A1C.

Table 5.4: Characteristics of Cat 4 Hyperglycemic Events by A1C Quartile Membership (N=216)[a,b]

	A1C Quartiles				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-value[c]**
N (%)	53 (24.5)	61 (28.2)	49 (22.7)	53 (24.5)	----
Events/ Week	2.8 (1.6)	4.3 (2.1)	6.0 (1.8)	6.1 (1.9)	< 0.0001
Event Duration, minutes	294.1 (66.7)	333.9 (86.0)	343.5 (55.9)	428.3 (111.9)	< 0.0001
Maximum Glucose Value, mg/dL	290.3 (9.8)	294.8 (12.9)	301.9 (12.4)	308.0 (16.4)	< 0.0001
Percent of All Minutes in Hyperglycemia Accounted for by Cat 4 Events	43.0 (14.5)	51.9 (15.7)	61.8 (12.0)	69.5 (11.9)	< 0.0001

[a]All statistics reported as Mean (SD).
[b]A1C quartiles calculated from 26-week A1C.
[c]p-value indicates ANOVA results.

Table 5.5: Regression Results for the Associations of A1C with Occurrence of Non-Severe Events, and with Percent Time in Hyperglycemia Accounted for by Cat 4 Events (n=216)

Primary Predictor: Occurrence of Non-Severe Events			
	B	**SE**	**p-value**
Occurrence of Non-Severe Events[a]	-0.04	0.004	< 0.0001
Total Weekly Events	0.02	0.01	< 0.05
BMI	0.005	0.01	0.6
Age	0.005	0.003	0.1
Gender	0.09	0.07	0.2
Study Site	-0.009	0.008	0.3
Primary Predictor: Percent time in Hyperglycemia Accounted for by Cat 4 Events			
% time in Hyperglycemia Accounted for by Cat 4 Events	0.03	0.002	<0.0001
Total Weekly Events	0.01	0.009	0.2
BMI	0.004	0.008	0.5
Age	0.008	0.003	<0.05
Gender	0.04	0.07	0.6
Study Site	-0.006	0.008	0.5

[a]Occurrence of non-severe events is defined as the percent of all hyperglycemic events accounted for by Cat1 and Cat2 events combined.

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CHAPTER 6:

PROACTIVE INSULIN BOLUSING IS ASSOCIATED WITH LOWER A1C AND REDUCED OCCURRENCE OF SEVERE HYPERGLYCEMIC EVENTS

Specific Aim: Collate insulin pump data and CGM data to describe how participants at different levels of A1C use insulin boluses to manage hyperglycemic events.

Hypothesis: *We hypothesize that a higher likelihood of proactive insulin bolusing is associated with lower A1C levels and a lower percent occurrence of severe hyperglycemic events.*

Introduction

Hyperglycemia (glucose >180 mg/dL) occurs regularly in most people with type 1 diabetes (T1D), and while having relatively few consequences in the moment, is associated with increased risk for long-term diabetes complications.[1,2] Appropriate dosing and timing of fast-acting insulin boluses is a key behavior for preventing and reducing hyperglycemia, as recommended by the American Diabetes Association (ADA).[3] Dosing the correct amount of insulin is a complicated calculation with material consequences that T1D must make in real-time: over-estimating the volume of insulin needed results in hypoglycemia, and under-estimating the volume of insulin results in sustained hyperglycemia. Continuous glucose monitors (CGM) provide T1D with their real-time glucose levels that can inform their insulin dosing decisions, and with alarms for hyperglycemia and hypoglycemia that indicate if corrective action needs to be taken.

In Chapter 5, we demonstrated that time spent in hyperglycemia (>180 mg/dL) increases significantly across A1C quartiles, and that participants in the highest A1C quartile experience twice as many Cat 4 hyperglycemic events (lasting >2 hours and glucose levels $\geq$ 250 mg/dL), lasting twice as long, as participants in the lowest A1C quartile. This suggests that those in better

glucose control take more proactive action to reduce their blood sugars to reduce the likelihood of severe hypoglycemic events [cumulative Cat 3 events (lasting >2 hours, but not exceeding 250 mg/dL) and Cat 4 events]. The major preventive action that T1Ds can take to avoid severe hyperglycemic events is to give themselves an extra bolus of insulin. The increased frequency and duration of severe hyperglycemic events among participants with higher A1Cs illustrates the importance of understanding how to prevent hyperglycemia from developing into severe hyperglycemic events in order to improve glucose outcomes.

In order to have the optimal amount of insulin on board, T1Ds are expected to calculate their current macronutrient intake, insulin sensitivity, any recent food intake that may still be impacting their glucose levels, recent fast-acting insulin injection volumes, basal insulin levels, and a number of idiosyncrasies that likely dictate that person's insulin dosing decisions.[4] The action of fast-acting insulin peaks at two hours,[5,6] so administering an insulin bolus within two hours of entering hyperglycemia indicates that the T1D judges that their current insulin on board is insufficient to return to euglycemia. When administering additional insulin boluses within two hours of a previous insulin bolus, T1Ds must consider "insulin stacking," which occurs when insulin from multiple boluses are active in a person's body, increasing the cumulative amount of fast-acting insulin on board. Insulin stacking is useful when used proactively to decrease glucose levels, but can result in dangerously low glucose levels if miscalculated or done accidentally. We define "proactive insulin bolusing" as insulin boluses that are administered within two hours of the beginning of a hyperglycemic event--- which, using our classification of hyperglycemic event severity, is any insulin bolus that occurs during a non-severe hyperglycemic event.

We use data from the REPLACE-BG (RBG) trial,[7] a study of 216 T1Ds who had excellent A1C levels throughout the trial and wore CGM and insulin pumps for the trial duration.

In Chapter 5, we demonstrated that all of these T1Ds were equally likely to have a hyperglycemic event. In this study, we use the categorization of hyperglycemic events developed in Chapter 5 and describe how insulin bolusing during hyperglycemic events varies by A1C quartile. We evaluate how proactive insulin bolusing is associated with the occurrence of severe hyperglycemic events, and overall glucose control measured by A1C. We hypothesize that a higher likelihood of proactive insulin bolusing will be associated with decreased occurrence of severe hyperglycemic events, and lower A1C.

Methods

Sample

This analysis examined data from 216 participants who recorded $\geq$ 14 days of CGM data and completed the baseline and end of study surveys. We chose 14 days as a minimum amount for CGM data because glucose metrics from a 14-day sampling period of CGM data have been shown to capture period prevalence of habitual glucose management and to correlate highly with glucose metrics from sampling periods of 30-days to 3 months.[8]

Study Design

This analysis used data from the REPLACE-BG trial[7] which has been previously described in the primary outcomes paper[7] and in Chapters 2, 3, and 4 of this dissertation. Briefly, this trial was a 6-month trial in which all participants used a Dexcom G4 Platinum CGM System (Dexcom, Inc., San Diego, CA) with an enhanced algorithm (Software 505), which measures glucose concentrations from interstitial fluid in the range of 40- 400 mg/dL every 5 minutes. The trial was conducted at 14 endocrinology practices in the U.S. that are members of the Type 1 Diabetes Exchange Network.

Study inclusion and exclusion criteria are described in Chapter 4. Of specific relevance is that potential participants were excluded based on the occurrence of any severe hypoglycemic event, an event in which the person required assistance from another person to treat their low glucose levels, or diabetic ketoacidosis within the past year. The study randomized 226 participants between May 2015 and March 2016.

Measures

Demographic and diabetes history information was collected via questionnaire at the initial screening visit. A venipuncture sample collected at week 26 was used to measure A1C by a central laboratory (Northwest Lipid Research Laboratories, University of Washington, by using the Diabetes Control and Complications Trial standardized analyzer (Tosoh Bioscience, South San Francisco, CA)). The 26-week A1C measurement was used in this analysis since it reflects the participants' glucose levels over the study period.

We utilize the measurement and categorization of hyperglycemic events that was developed in Chapter 5, combining cat 1 and cat 2 events into a "non-severe hyperglycemic events" category and combining cat 3 and cat 4 events into a "severe hyperglycemic events" category. For each participant's CGM data over the entire study period, we utilize the mean frequency of total hyperglycemic events per week, percent of total hyperglycemic events accounted for by severe events, percent of total minutes in hyperglycemia accounted for by severe events; and mean duration of severe events. We also utilize aggregate glucose metrics measured in Chapter 5, including percent time in hyperglycemia (> 180 mg/dL) and glucose coefficient of variation.

We analyze the insulin pump data to describe the frequency and volume of administered insulin boluses. In order to evaluate if an insulin bolus was administered during a hyperglycemic

event, we matched the insulin pump data and CGM data by date and timestamp. The percent of hyperglycemic events in which an insulin bolus was administered was calculated for each participant for each event severity category, and for all non-severe hyperglycemic events (defined as the *likelihood of administering* a *proactive insulin bolus*).

Analysis

We performed ANOVA to determine how mean daily bolus frequency, mean volume of insulin injected per bolus, and *likelihood of administering a proactive bolus* varied within standard demographic categories. Descriptive statistics were generated as means with standard deviations for continuous variables, and frequencies with percentages for categorical variables.

We categorized participants into quartiles of A1C measured at the 26-week time-point and performed ANOVA to determine if percent occurrence of severe hyperglycemic events, mean daily minutes in hyperglycemia, percent of minutes in hyperglycemia accounted for by severe events, and mean duration of severe events varied significantly across A1C quartiles. To quantify differences in insulin bolusing behavior across A1C quartiles, we performed ANOVA for the following variables: daily number of boluses, total insulin bolus volume per day, likelihood of administering a proactive bolus, and the percent of Cat3 and Cat4 events (separately) in which an insulin bolus was administered. For each of the above- mentioned variables, we also performed linear regression with 26-week A1C to test for linearity.

We conducted univariable and multivariable linear regressions to examine the association of the *likelihood of proactive insulin bolusing* with 1) the percent occurrence of severe hyperglycemic events and 2) A1C. *Likelihood of proactive insulin bolusing* was the primary predictor variable in both models, and separate parsimonious multivariable linear regression models were built for each outcome. Both models included study site, age, and gender as

covariates to control for the multi-cohort nature of the population and multi-site nature of the study. BMI and glucose coefficient of variation were tested as covariates based on their univariate association with the model outcome. Variables with p-values <0.2 in univariable models were considered as covariates in multivariable models, where p-values <0.05 were considered statistically significant. SAS 9.4 was used for all analyses.

Results

A total of 216 participants were included in the analysis: 50% were female, 94% were white, 56% were over 40 years old, 56% had diabetes for more than 20 years, and 66% were overweight or obese (BMI > 25 kg/m^2) (Table 6.1). Seventy-four percent of participants reported never experiencing DKA, and the remaining participants reported not experiencing more than one DKA episode in the previous year.

Each participant recorded a mean (SD) of 162.2 (25.3) days of CGM data during the study period. The mean daily frequency of insulin boluses ranged from 4.5- 4.9 across demographic categories; there were no significant differences between categories of the same demographic variables (Table 6.1). The mean volume of insulin injected/ bolus ranged from 2.7- 4.7 units across demographic categories. Participants with a BMI ≤25 kg/m2 vs. >25 kg/m^2 injected a mean (SD) volume of 2.7 (1.5) units vs. 4.5 (2.5) units per insulin injection, and female vs. male participants injected a mean (SD) volume of 3.2 (1.6) units vs. 4.7 (2.5) units per insulin injection (both p-values <0.05). Participants with an A1C ≤ 7% vs. >7% injected a mean (SD) volume of 3.6 (2.0) vs. 4.2 (2.5) units per insulin injection (p <0.05) (Table 6.1). The likelihood of administering a proactive bolus ranged from 21.8% to 27.3%, and only varied significantly between participants with an A1C ≤7% vs. >7% (27.3% (12.3%) vs. 21.8% (9.3%), p <0.0001).

Participants in each higher A1C quartile spent a mean (SD) 333.2 (169.9), 426.1 (140.8), 522.3 (149.0), and 631.6 (183.8) minutes per day in hyperglycemia (p-value for linearity <0.0001) (Table 6.2). The percent of all hyperglycemic events accounted for by severe events increased significantly across the sequential A1C quartiles [33.8% (9.7%), 40.3% (7.8%), 45.3% (7.7%), and 50.9% (7.6%), p-value for linearity <0.0001], as did the percent of all hyperglycemic minutes accounted for by severe events [71.5% (13.8%), 79.9% (8.1%), 83.7% (7.2%), and 88.79% (4.4%), p-value for linearity <0.0001], and the mean duration of severe events [242.7 (45.5), 272.0 (48.1), 277.8 (33.2), and 325.1 (65.5) minutes, p-value for linearity <0.0001] (Table 6.2).

The daily number of insulin boluses was significantly different between A1C quartiles (p-value for linearity <0.01), with A1C quartiles 1 and 3 injecting at a higher frequency--- a mean 5.3 (2.1) and 4.9 (1.6) insulin boluses per day, respectively (Table 6.3). A1C quartiles 2 and 4 injected a mean 4.3 (1.5) and 4.1 (1.5) insulin boluses per day, respectively. The total daily volume of insulin injected varied significantly between A1C quartiles (p <0.001), with participants in A1C quartiles 1 and 4 injecting a greater volume of insulin per day--- 17.9 (10.4) and 18.3 (10.9) International Units (IU), respectively. Participants in A1C quartiles 2 and 3 injected a mean of 15.2 (8.8) and 16.7 (8.2) IU of insulin per day. The mean (SD) likelihood of proactive insulin bolusing decreased significantly across increasing A1C quartiles [31.5% (12.6%), 23.1% (10.0%), 23.8% (9.7%), and 19.3% (8.6%), p- value for linearity <0.0001], as did the mean (SD) percent of Cat 3 events in which an insulin bolus was administered [74.5% (18.1%), 65.1% (20.0%), 64.6% (17.8%) p- value for linearity < 0.0001] (Table 6.3). The percent of cat 4 events in which a bolus was administered did not vary significantly across A1C quartiles (p-value for linearity of 1.0).

In conducting the multiple linear regression analysis for the outcome *percent occurrence of severe hyperglycemic events* and primary predictor *likelihood of proactive insulin bolusing,* our final, parsimonious model adjusted for age, gender, study site, BMI, and glucose coefficient of variation. Glucose coefficient of variation and BMI had significant associations with the outcome in both univariate in multivariate models, and were retained in the final model. In the final model, we found the *likelihood of proactive insulin bolusing* to be significantly, inversely associated with the *percent occurrence of severe hyperglycemic events* (beta= -0.4, SE=0.05, $p < 0.0001$) (Table 6.4); and glucose coefficient of variation and BMI were significantly, positively associated with percent occurrence of severe hyperglycemic events (BMI: beta= 0.3, SE=0.1, $p < 0.05$; glucose coefficient of variation: beta= 0.5, SE= 0.1, $p < 0.001$).

In conducting the multiple linear regression analysis for the outcome *A1C* and the primary predictor *likelihood of proactive insulin bolusing*, our final, parsimonious model adjusted for BMI, age, gender, and study site. Glucose coefficient of variation did not have a significant univariate association with A1C and was not included in the multivariable model. BMI had a significant univariate association with A1C and was retained in the final multivariate model because it met criteria for borderline significance ($p < 0.1$). In the final model (Table 6.4), the likelihood of proactive insulin bolusing was significantly, inversely associated with A1C (beta= -0.02, SE =0.004, $p < 0.0001$).

Discussion

In this study of how of T1Ds utilize insulin boluses to manage CGM-measured hyperglycemic events, we identified that participants in lower quartiles of A1C have a higher likelihood of proactive insulin bolusing compared to participants in higher A1C quartiles. We

found that a higher likelihood of proactive insulin bolusing is significantly associated with a lower percent occurrence of severe hyperglycemic events, and lower A1C.

Across all levels of glucose control, participants injected insulin about four to six times per day. The total volume of insulin injected per day was highest, and nearly identical, in A1C quartiles 1 and 4 [17.9 (10.4) IU vs. 18.3 (10.9) IU]. Participants in A1C quartile 1 injected significantly more insulin boluses per day than participants in A1C quartile 4 [5.3 (2.1) vs. 4.1 (1.5) daily injections]. Additionally, participants in A1C quartile 1 administered proactive insulin boluses in a mean (SD) of 31.5 % (12.6%) of their non-severe hyperglycemic events, compared to 19.3% (8.6%) for participants in A1C quartile 4.

When looking at these insulin bolusing patterns in the context of glucose control, we see that participants in the lowest A1C quartile spend about half as much time in hyperglycemia as participants in the highest A1C quartile [333.2 (169.9) minutes vs. 631.6 (183.8) minutes], and experience 30 percent fewer severe hyperglycemic events as participants in the highest A1C quartile [33.8% (9.7%) vs. 50.9% (7.6%)]. Additionally, we see that for the severe hyperglycemic events that do occur, the mean duration is more than an hour shorter for participants in A1C quartile 1 vs. 4. This suggests that while participants in different A1C quartiles may use similar total daily volumes of insulin, participants in the lowest A1C quartile inject smaller and more frequent boluses, are more likely to bolus proactively than participants in higher A1C quartiles, and are able to spend significantly less time in hyperglycemia than participants in higher A1C quartiles.

Our multivariate model that assessed the association of *percent occurrence of severe hyperglycemic events* with *the likelihood of proactive insulin bolusing* indicated that for each 2.5% increase in likelihood of proactive bolusing, the percent occurrence of severe

hyperglycemic events decreases by 1%. This indicates that participants who have a higher likelihood of proactively bolusing are able to keep more of their hyperglycemic events from becoming severe, compared to participants who are less likely to proactively bolus. Additionally, for every 2 unit increase in glucose coefficient of variation, the percent occurrence of severe hyperglycemic events increases by 1%. This model also indicates that for every 3.3 kg/m^2 increase in BMI, *percent occurrence of severe hyperglycemic events* increases by 1%.

Our multivariate model that assessed the association of A1C with *the likelihood of proactive insulin bolusing* indicated that for each 12.5% increase in likelihood of proactive insulin bolusing, A1C value decreases by 0.25%. This indicates that a higher likelihood of proactively bolusing has a material impact on A1C, the clinical standard for glucose control. This association, in conjunction with our finding that the total daily volume of insulin is nearly identical between the lowest and highest A1C quartiles, suggests that the timing of insulin injections, and not the total volume injected, is crucial to optimizing glucose control, as measured by A1C.

The glucose coefficient of variation represents how widely a person's glucose values fluctuate around their mean glucose, and was positively and significantly associated with the percent occurrence of severe hyperglycemic events in final models. These associations indicate that participants who have larger fluctuations in their glucose have a higher likelihood of hyperglycemic events becoming severe, and that glucose coefficient of variation is an indicator of poor glucose control.

In this study we define administering an insulin bolus during a non-severe hyperglycemic event to be "proactive" because the T1D likely still has insulin on board from a previous insulin bolus at this time, but is judging that they will require more insulin to return to euglycemia. The

T1D is likely utilizing information from their CGM, like current glucose value and rate of change, to decide that they require additional insulin even though their most recent dose is still active, and that injecting an additional insulin dose is not likely to drive their glucose levels low. Even though not all non-severe hyperglycemic events will require an additional insulin bolus since the current insulin bolus on board may be adequate to return glucose levels to euglycemia, we use the percent of non-severe hyperglycemic events in which a bolus was administered as a proxy for *proactive insulin bolusing* behavior as this metric indicates a person's attentiveness to high glucose levels and likelihood to take action to return to euglycemia.

While this analysis was useful in describing the significant relationships between proactive insulin bolusing and percent occurrence of severe hyperglycemic events, and proactive insulin bolusing and A1C, it points toward additional research questions that can be evaluated with this dataset. Because this dataset contains CGM data on the 5-minute level, and all insulin boluses administered during the study period, future analyses can use the CGM and insulin pump data to assess the context of a T1D's glucose levels when an insulin bolus is administered. This may include measuring the glucose value and glucose rate of change when a bolus is administered, and calculating the amount of time that has elapsed since the last insulin bolus was administered and since leaving euglycemia. Future analyses can also calculate the amount of time it takes to return to euglycemia, and how the glucose trend changes after an insulin bolus is administered.

A limitation of this study is that, while we have rich CGM and insulin pump data, we do not have information on food intake or physical activity, which are key behaviors that impact glucose levels. Additionally, this dataset does not provide information on insulin basal rates,

which account for a large portion of insulin on board and are an integral part of glucose management.

Our data indicate that that administering proactive insulin boluses is key to preventing the occurrence of severe hyperglycemic events. Additionally, we show that an increased likelihood of proactive insulin bolusing is significantly associated with lower A1C levels, which is the clinical standard for measuring glucose control. This paper is novel in its concatenation of CGM data in its continuous form and insulin pump data to enhance understanding of the occurrence and management of hyperglycemic events across participants with different A1C levels, and suggests the importance of promoting proactive insulin boluses in order to optimize diabetes management.

Table 6.1: Mean Daily Frequency and Volume of Insulin Boluses, and Likelihood of Administering Proactive Insulin Boluses, by Demographic Categories (N=216)[a,b]

	N (%)	Mean Daily Bolus Frequency	Mean Volume of Insulin Injected/ Bolus	Likelihood of Administering Proactive Bolus
Age, years				
≤ 40 years	96 (44)	4.8 (2.0)	4.1 (2.3)	25.0 (12.6)
> 40 years	120 (56)	4.6 (1.6)	3.8 (2.3)	23.9 (9.9)
BMI (kg/m2)				
≤25 kg/m2	73 (34)	4.9 (1.8)	**2.7 (1.5)**	25.2 (11.1)
>25 kg/m2	143 (66)	4.5 (1.7)	**4.5 (2.5)**	24.0 (11.2)
Gender				
Female	108 (50)	4.6 (1.8)	**3.2 (1.6)**	24.6 (11.6)
Male	108 (50)	4.7 (1.8)	**4.7 (2.7)**	24.1 (10.8)
A1C*				
≤ 7%	102 (47)	4.8 (1.9)	**3.6 (2.0)**	**27.3 (12.3)**
> 7%	114 (53)	4.5 (1.6)	**4.2 (2.5)**	**21.8 (9.3)**
Income				
<$50,000	23 (11)	4.9 (2.4)	3.2 (2.0)	24.3 (12.8)
$50,000- $100,000	55 (25)	4.8 (1.8)	3.5 (1.6)	25.0 (12.8)
>$100,000	84 (39)	4.5 (1.6)	3.5 (1.6)	25.0 (12.3)
Unknown/ Missing	54 (25)	4.6 (1.7)	4.0 (2.3)	24.1 (11.8)
Ethnicity				
White	203 (94)	4.7 (1.7)	3.9 (2.4)	24.2 (11.0)
Other/ Unknown	13 (6)	4.9 (2.0)	4.6 (2.0)	27.9 (12.7)
Duration of Diabetes				
≤ 20 years	96 (44)	4.7 (2.0)	4.0 (2.7)	23.5 (11.3)
>20 years	120 (56)	4.6 (1.5)	3.9 (2.1)	25.1 (11.0)
History of Severe Hypoglycemia				
Yes	76 (35)	4.8 (1.7)	3.9 (2.0)	24.9 (11.3)
No	140 (65)	4.6 (1.8)	3.9 (2.5)	24.1 (11.1)
History of DKA				
Yes	57 (26)	4.6 (1.8)	3.9 (2.0)	25.0 (11.9)
No	159 (74)	4.7 (1.8)	3.9 (2.5)	24.2 (10.9)

[a] Proactive insulin boluses defined as: insulin boluses administered during non-severe hyperglycemic events.
[b] All variables are reported as mean (SD).
*A1C measured at 26-week visit (end of study).

Table 6.2: Characteristics of Hyperglycemia and Severe Hyperglycemic Events by A1C Quartile (n=216)[a,b]

	A1C Quartile				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-value[e]**
N (%)	53 (24.5)	61 (28.2)	49 (22.7)	53 (24.5)	----
A1C Range (%)	5.2-6.5	6.6- 7.1	7.2- 7.4	7.5- 10.2	----
Total Events/ Week	15.0 (4.3)	18.1 (4.0)	20.7 (3.9)	18.0 (3.5)	< 0.0001
Percent Occurrence of Severe Events[c]	33.8 (9.7)	40.3 (7.8)	45.3 (7.7)	50.9 (7.6)	<0.0001
Daily minutes in Hyperglycemia[d]	333.2 (169.9)	426.1 (140.8)	522.3 (149.0)	631.6 (183.8)	< 0.0001
% of Minutes in Hyperglycemia Accounted for by Severe Events	71.5 (13.8)	79.9 (8.1)	83.7 (7.2)	88.7 (4.4)	<0.0001
Mean Duration of Severe Events, minutes	242.7 (45.5)	272.0 (48.1)	277.8 (33.2)	325.1 (65.5)	<0.0001

[a]All values reported as Mean (SD).
[b]Severe hyperglycemic events defined as events lasting longer than 2 hours.
[c]Percent of total hyperglycemic events accounted for by severe events.
[d]Hyperglycemia defined as glucose values >180 mg/dL.
[e]p-value is calculated from test for linearity with 26-week A1C.

Table 6.3: Insulin Bolusing Characteristics by A1C Quartile (n=216)[a]

	A1C Quartile				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-value[b]**
Daily Number of Boluses	5.3 (2.1)	4.3 (1.5)	4.9 (1.6)	4.1 (1.5))	< 0.01
Total Insulin Bolus Volume/ Day, IU[c]	17.9 (10.4)	15.2 (8.8)	16.7 (8.2)	18.3 (10.9)	< 0.001
% Likelihood of Proactive Bolusing[d]	31.5 (12.6)	23.1 (10.0)	23.8 (9.7)	19.3 (8.6)	<0.0001
% Cat3 Events with Bolus Administered[e]	74.5 (18.1)	65.1 (20.0)	64.6 (17.8)	60.3 (17.8)	<0.0001
% Cat4 Events with Bolus Administered[f]	86.5 (14.2)	84.0 (20.3)	88.9 (11.7)	84.8 (17.8)	1.0

[a]All values reported as Mean (SD).
[b]p-value is calculated from test for linearity with 26-week A1C.
[c]Insulin volume unit is IU (International Unit).
[d]The likelihood of proactive bolusing is the percent of all non-severe (<2 hours) hyperglycemic events in which an insulin bolus was administered.
[e]Cat 3 events are >2 hours and the maximum glucose value is 180- 250 mg/dL.
[f]Cat4 events are >2 hours and the maximum glucose value is >250 mg/dL.

Table 6.4: Regression Results for the Associations of Likelihood of Proactive Insulin Bolusing with Percent Occurrence of Severe Hyperglycemic Events, and A1C (n=216)[a,b]

Outcome: Percentage of Severe Hyperglycemic Events			
	B	**SE**	**p-value**
Likelihood of Proactive Bolusing	-0.4	0.05	<0.0001
Glucose Coefficient of Variation	0.5	0.1	<0.001
BMI	0.3	0.1	<0.05
Age	-0.06	0.04	0.2
Gender	0.4	1.2	0.8
Study Site	0.2	0.1	0.2
Outcome: A1C			
Likelihood of Proactive Bolusing	-0.02	0.004	<0.0001
BMI	0.02	0.01	0.07
Age	0.00009	0.003	0.8
Gender	0.1	0.09	0.1
Study Site	-0.003	0.01	0.8

[a]The likelihood of proactive bolusing is the percent of all non-severe hyperglycemic events in which an insulin bolus was administered.
[b]Hyperglycemic events in which glucose was >180 mg/dL for <2 hours are defined as "non-severe." Hyperglycemic events in which glucose was >180 mg/dL for >2 hours are defined as "severe."

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CHAPTER 7:

CONCLUSION AND FUTURE OF CONTINUOUS GLUCOSE MONITORING

The questions addressed in this dissertation relate to understanding the glucose management practices occurring in the current population of people with type 1 diabetes in the United States who use continuous glucose monitors. The participants in this dataset, 216 people with well-controlled diabetes from the Replace-BG trial, administered insulin with insulin pumps and monitored their glucose with continuous glucose monitors (CGM). CGM provides a person with their glucose level every five minutes and has been reported to improve diabetes management outcomes. Given the changing landscape of glucose monitoring and available diabetes treatments, we seek to describe the CGM data and glucose trends this population sees and responds to in real-time, to measure the glucose management behaviors occurring in the population, and to evaluate how these glucose management behaviors relate to CGM- derived glucose metrics.

Measurement of Hypoglycemia- Related Behaviors

Specific Aim: To understand which items from the Hypoglycemia Fear Survey- Behavior (HFS-B) scale are useful for measuring currently promoted diabetes management behaviors, and to derive scales that measure unique hypoglycemia-related behavior constructs.

Hypothesis: *The HFS-B will measure more than one domain of hypoglycemia-related behavior.*

In Chapter 3, we aimed to 1) understand which HFS-B items are useful for measuring currently promoted diabetes management behaviors, and 2) derive scales that measure hypoglycemia-related behavior constructs for use in predicting the occurrence of hypoglycemic events in Chapter 4. Since a number of improvements in treatments and glucose monitoring technology that have happened since the 1980s, when the HFS-B was created, we hypothesized

that the HFS-B would measure more than one domain of hypoglycemia-related behavior in the RBG population.

Compared to past norms in diabetes management, which required detecting low glucose through feeling the symptoms of hypoglycemia or measuring blood glucose through fingerstick monitoring, CGM serves as a safety net for detecting and alerting people of hypoglycemia. Since CGM is becoming widely adopted for glucose monitoring and management, it is important to understand how to measure hypoglycemia-related behaviors in this population.

This analysis guided the formation of three scales that measure distinct constructs of hypoglycemia-related behaviors: hypoglycemia avoidance behavior, hypoglycemia reaction behavior, and hypoglycemia prevention behavior. these scales allow for specific measurement of how hypoglycemia-related behaviors predict hypoglycemic events. The three scales produced by this analysis were used in Chapter 4 to evaluate the relationship between hypoglycemia-related behaviors and hypoglycemic events.

CGM- Measured Hypoglycemic Events and Hypoglycemia Behavior Constructs

Specific Aim: To describe the frequency and severity of hypoglycemic events in a group of people with well-controlled type 1 diabetes, and relate these measures to scores on hypoglycemia- related behavioral scales.

Hypothesis: *Participants who score lower versus higher on the hypoglycemia prevention behavior scale will experience a higher percent occurrence of moderate hypoglycemic events and a longer duration of moderate hypoglycemic events.*

In Chapter 4, our analysis of CGM- measured hypoglycemic events, we aimed to describe the occurrence of mild (minimum glucose value: <70 mg/dL and >50 mg/dL) and moderate (minimum glucose value ≤50 mg/dL) hypoglycemic events in the RBG population and

to evaluate how hypoglycemia-related behavior constructs predict the frequency and duration of moderate hypoglycemic events. We hypothesized that higher levels of hypoglycemia prevention behavior would be associated with fewer and shorter moderate hypoglycemic events. This description of CGM- measured hypoglycemic events provides a snapshot of how hypoglycemic events occur in a population of well-controlled T1D, and the analysis of how hypoglycemia-related behavior constructs predict hypoglycemic events will identify which behaviors have a material impact on glucose values.

We identified that hypoglycemic events were frequent for all T1D regardless of their A1C level, demographics, or level of hypoglycemic avoidance, reaction, and prevention behavior. The mean frequency of weekly mild hypoglycemic events ranged from 4.3- 6.8 across demographic categories, and the mean frequency of weekly moderate hypoglycemic events ranged from 1.4- 2.2. The level of hypoglycemia prevention behavior was the main variable that differentiated the frequency and duration of moderate hypoglycemic events. The mean duration of moderate hypoglycemic events was 6 minutes longer among participants in the lower category for hypoglycemia prevention behavior (defined by the median score) compared to participants in the higher category (73.0 vs. 66.0 minutes).

Our regression results indicate that participants who are more likely to engage in hypoglycemia prevention behaviors--- carrying fast-acting sugar in case of hypoglycemia, avoiding exercise if glucose is already low, and self-monitoring glucose levels--- have a significantly lower likelihood of mild hypoglycemic events becoming moderate. In the case that a hypoglycemic event is moderate, these participants are able to recover from hypoglycemia significantly faster than participants who are less likely to engage in hypoglycemia prevention behaviors.

This analysis illustrates the advantage of measuring glucose control with CGM as opposed to A1C in order to capture the frequency and duration of hypoglycemic events. Additionally, this paper suggests the importance of promoting hypoglycemia prevention behaviors to mitigate the risks of hypoglycemia. Next steps in studying the relationship between behaviors and CGM-measured glucose management will be the creation of a scale that measures behaviors that are performed with the intent of preventing hypoglycemia *and hyperglycemia.* Measuring the behaviors that impact both sides of the euglycemic range will allow for the prediction of hypoglycemic and hyperglycemic event duration and frequency, glucose coefficient of variation, and combinations of behaviors that maximize time spent in euglycemia.

Categorization of Hyperglycemic Event Severity and Relationship with A1C

Specific Aim: Develop categories of severity for hyperglycemic events and describe how measures of hyperglycemic events relate to A1C.

Hypothesis: *Participants at higher levels of A1C will experience more frequent hyperglycemic events and a higher percent of total hyperglycemic events that are severe.*

In Chapter 5, our analysis of CGM- measured hyperglycemic events, we aimed to categorize hyperglycemic events by severity, describe patterns in the severity of hyperglycemic events that are experienced by participants at different levels of A1C, and explore how different measures that describe hyperglycemia relate to improved A1C levels. We hypothesized that we would be able to identify metrics that are powerful predictor of A1C levels. This study is important because it relates characteristics of hyperglycemic events, which are observed in real-time by T1D, to A1C, which is the current clinical standard for measuring glucose control. The single metric of hyperglycemia that is identified as a strong predictor of A1C can be used as an

end-point in future studies in order to identify glucose management practices that minimize exposure on this metric.

To categorize the severity of hyperglycemic events, we utilize the ADA definition of moderate hyperglycemia (180 to < 250 mg/dL) and severe hyperglycemia (>250 mg/dL)[8], in conjunction with their recommendation that meal-related hyperglycemic events should not last more than 2 hours. We created the following 4 categories of hyperglycemic events: Category 1 = duration of less than 30 minutes; Category 2= duration of 30- 119.9 minutes; Category 3= duration $\geq$ 2 hours, maximum glucose value < 250 mg/dL; Category 4= duration $\geq$ 2 hours, maximum glucose value $\geq$ 250 mg/dL. A total of 101,020 hyperglycemic events occurred during the study period, over all participants. These events included many instances of each of the severity categories: 24% were Cat 1, 33% were Cat 2, 17% were Cat 3, and 26% were Cat 4.

The mean frequency of weekly hyperglycemic events per participant increased significantly across higher A1C quartiles; even in the lowest A1C quartile, there were an average of 15 hyperglycemic events every week during the study. Participants in the highest A1C quartile spent 2.5 times more time in hyperglycemia than participants in the lowest A1C quartiles (10.6 hours/day vs. 4.3 hours/day). The increase in daily time in hyperglycemia across increasing A1C quartiles, in conjunction with the increasing percent of all time in hyperglycemia accounted for by Cat 4 events, highlights the large amount of time that participants in higher A1C quartiles spend in Cat 4 events. Alternatively, participants in A1C quartiles 1 and 2 experience a significantly higher percentages of non-severe hyperglycemic events than participants in higher A1C quartiles.

Our regression results indicated that experiencing higher percentages of non- severe events (Cat 1 and Cat 2) was significantly associated with lower A1C, and a smaller percent of

time spent in hyperglycemia accounted for by Cat 4 events was significantly associated with lower A1C. The metric that we identified as a powerful predictor of A1C is the *percent of time spent in hyperglycemia accounted for by Cat 4 events.*

This analysis adds to the field of diabetes management by providing a snapshot of how hyperglycemia is experienced by T1D at varying levels of good glucose control. We show that everyone experiences hyperglycemia, and that managing hyperglycemic events to be non-severe (< 2 hours) and minimizing the amount of time spent in severe hyperglycemia is related to lower A1C levels. This information can be used to inform the glucose management goals and real-time decisions of T1Ds, and also used to direct discussions between T1Ds and their diabetes care providers. Our findings point to the importance of understanding which glucose management behaviors minimize the occurrence and severity of participants' hyperglycemic events. Next steps should evaluate the relationships between metrics of hyperglycemic events and the ADA-suggested behaviors for glucose management: insulin dosing, physical activity, food choices, and emotional wellness.

Proactive Insulin Bolusing as a Glucose Management Behavior

Specific Aim: Collate insulin pump data and CGM data to describe how participants at different levels of A1C use insulin boluses to manage hyperglycemic events.

Hypothesis: *We hypothesize that a higher likelihood of proactive insulin bolusing will be associated with improved glucose control.*

In Chapter 6, our analysis of insulin bolusing during hyperglycemic events, we aimed to describe insulin bolusing behaviors of participants at different levels of A1C, including daily frequency and total daily volume of insulin boluses and likelihood for administering proactive insulin boluses. We defined "proactive insulin bolusing" as the administration of an insulin bolus

within two hours of the beginning of a hyperglycemic event--- by our hyperglycemic event severity classification, this is an insulin bolus administered during a non-severe hyperglycemic event. We utilized the hyperglycemic event severity classification developed in Chapter 5, and evaluated how proactive insulin bolusing is related to the occurrence of severe hyperglycemic events and to A1C. We hypothesized that a higher likelihood of proactive insulin bolusing will be associated with decreased occurrence of severe hyperglycemic events and with lower A1C. This analysis is important because it evaluates proactive insulin bolusing as a glucose management behavior that may drive the occurrence of fewer severe hyperglycemic events and lower A1C.

Across all levels of A1C, participants injected insulin a mean of four to six times per day. The total volume of insulin injected per day was highest, and nearly identical, in A1C quartiles 1 and 4 (17.9 (10.4) units vs. 18.3 (10.9) units). Participants in A1C quartile 1 injected the same amount of total insulin volume over a significantly higher number of insulin boluses per day than participants in A1C quartile 4 (5.8 (SD) vs. 4.4 (SD) daily injections, respectively). Additionally, participants in A1C quartile 1 administered proactive insulin boluses in 31.5 % (12.6%) of their non-severe hyperglycemic events, compared to 23.1% (10.0%), 23.8% (9.7%), and 19.3% (8.6%) for participants in A1C quartiles 2, 3, and 4, respectively. This suggests that the timing of insulin bolus administration is an important factor in glucose control since participants in different A1C quartiles can use a similar total volume of insulin per day but achieve varying glucose outcomes.

Our regression results indicated that that a higher likelihood of administering proactive insulin boluses is significantly associated with a lower occurrence of severe hyperglycemic events and with lower A1C levels. This analysis adds to the field of diabetes management by

setting a precedent for concatenating continuous CGM data with insulin pump data to enhance understanding of the occurrence and management of hyperglycemic events across participants with different A1C levels. Our findings that proactive insulin bolusing is associated with improved glucose control suggests the importance of promoting proactive insulin bolusing as a diabetes management behavior, and can also inform the development of automated insulin delivery systems.

Next steps should include studying the glucose context in which proactive insulin bolusing is appropriate. This may include measuring the glucose value and glucose rate of change when an insulin bolus is administered, calculating the amount of time that has elapsed since the last insulin bolus was administered and since leaving euglycemia, and measuring the volume of insulin that is bolused. Outcomes can include the likelihood of the hyperglycemic event progressing to a severe event, and also the likelihood of the insulin bolus resulting in hypoglycemia. Additional datasets that are created to study insulin bolusing as a glucose management behavior should include information on physical activity, food choices, and basal insulin rates, as these factors all have material effects on glucose levels.

Conclusion

Our analyses indicate that in this population of T1Ds who have well-controlled diabetes and use contemporary glucose monitoring and insulin administration technology to manage their diabetes (CGMs and insulin pumps), participants at all levels of A1C experience frequent hypoglycemic and hyperglycemic events. We learned that a person's likelihood of engaging in *hypoglycemia prevention behaviors* significantly predicts the occurrence and duration of moderate hypoglycemic events. We also learned that experiencing larger percentages of non-severe hyperglycemic events, and spending less of time in hyperglycemia in the most severe

hyperglycemic events, are significantly associated with lower A1C. Our analysis that concatenated CGM data and insulin pump data indicated that an increased likelihood of administering proactive insulin boluses is significantly associated with a lower occurrence of severe hyperglycemic events and a lower A1C.

The Replace-BG dataset is unique because it provides 6-months of CGM and insulin pump data for a contemporary population who utilize current advanced technologies to manage their diabetes. The behaviors that we identified as predictors of moderate hypoglycemia and severe hyperglycemia can be leveraged as important behaviors to intervene on in future scientifically based glucose management programs.

Future of CGM

The data captured by CGM is unique in that it measures a person's level of glucose control and also reflects behaviors and experiences that the person engages in, such as physical activity, eating certain foods, stress, sleep, etc. Managing type one diabetes is a challenging task-- the difference in volume between a correct insulin dose and a lethal insulin dose is often minute. T1Ds are assigned the lifelong duty of paying close attention to their physiology and behaviors in order to decipher what behaviors are best for their glucose management. The diabetes management behaviors that diabetes care providers readily discuss are food choices, physical activity, and insulin dosing, but T1D learn through experience that reliance on those behaviors alone will not result in optimal glucose outcomes.

The moderate hypoglycemic events and severe hyperglycemic events defined in this dissertation are often the best teachers of what works (and does not work) for a person's glucose management. While CGM alarms are useful alerts for when action is required to maintain safe glucose levels, the shaking hands and sweaty clothes that a T1D exiting a moderate

hypoglycemic event feels is likely to instigate an evaluation of what caused that hypoglycemic event and how they can avoid it in the future. In this sense, CGM data captures the glucose events that impact a person's quality of life, define their days as a good or bad "diabetes day," define their level of "diabetes distress," and serve as teachers for which diabetes management behaviors work in what contexts of their physiology.

CGM is rapidly becoming a norm in diabetes management, which will allow more T1D to base their diabetes management decisions on real-time glucose trend data and to discuss their behaviors and CGM data with eachother and their diabetes care providers. In order to support this phenomena, it is important to have an understanding of what "normal" CGM-measured hypoglycemia, hyperglycemia, and euglycemia look like in T1D--- which was an objective of this dissertation. Additionally, behavioral recommendations are currently being developed for how to manage specific glucose scenarios.

The CGM datastream is an important input and output component for the automated glucose management systems that are rapidly developing. The Dexcom G6 CGM alerts for "predicted urgent low glucose (glucose <55 mg/dL)" based on CGM data alone. This illustrates the current descriptive state of CGM-derived information to consumers--- instead of providing a recommendation to "eat fast-acting carbohydrates" for hypoglycemia or "go on a walk" for hyperglycemia, current systems are restricted by the Food and Drug Administration (FDA) to deliver a data-centric description of glucose values that the T1D can interpret for the appropriate behavior. Insulin pumps are increasingly being integrated with CGM systems and can provide recommendations on basal insulin rates and insulin bolus doses using patient-input physical activity levels, food consumption, and estimated insulin: carbohydrate ratio. This is an example

of user-input information, machine-delivered recommendation, and a user-delivered insulin bolus, which still leaves the diabetes management decisions in the T1D's hands.

Fully automated insulin delivery (AID) systems, which effectively remove any human decision making from insulin administration, are in development and leverage the CGM datastream to inform insulin administration decisions and to constantly measure the outcomes of those decisions. While proprietary, it can be imagined that AID systems calculate insulin to be administered as a basal-rate and as insulin boluses based on insulin-on-board, glucose trends from the immediate past, glucose trajectory, and any other information that can be garnered from the insulin and CGM datastreams. While full AID systems are still being piloted, the T:Slim insulin pump recently integrated a Dexcom CGM and suspends administration of basal-rate insulin when it predicts that the person is at risk for hypoglycemia. This illustrates that current AID systems are restricted from taking action to prevent hypoglycemia (ie. Suspending insulin delivery), but still perceive the administration of insulin boluses as risky--- something for the T1D to do.

As automated glucose management systems and automated insulin delivery systems become more confident in their recommendation and insulin delivery algorithms, we can expect these systems to take on more diabetes management decisions, and thus relieving T1D of their constant monitoring and decision making. Until then, CGM is a life-saving tool for T1D--- acting as a "safety net" by alarming for low glucose levels--- and is tool for facilitating self-reflection by recording the glycemic events that represent a person's behaviors, experiences, and diabetes management decisions.