T1D Exchange

SEVERE HYPOGLYCEMIA IN OLDER ADULTS WITH TYPE 1 DIABETES

A Study to Identify Factors Associated with the Occurrence of Severe Hypoglycemia in Older Adults with T1D

A T1D Exchange Clinic Network Protocol

Version 2.0

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CHAPTER 1: INTRODUCTION

1.1 Background Information

Severe hypoglycemia (SH) is a major acute complication of type 1 diabetes (T1D). In the most severe cases, seizure or loss of consciousness can occur and uncommonly, even death. In addition to altered mental status, SH is associated with an increased risk for falls, car accidents and other injuries.

The T1D Exchange clinic registry is collecting core clinical and laboratory data on more than 25,000 adults and children with T1D (1). As part of the data collection at enrollment into the registry, information was collected on SH events associated with seizure or loss of consciousness. In adults $\geq$26 years old, one or more SH events within 12 months was reported by 11.9%. The frequency of SH increased with older age ($p<0.001$). However, the age effect was largely explained by T1D duration. SH frequency increased with longer T1D duration, with the 12-month frequency of one or more events being 18.6% in participants with T1D for $\geq$40 years. With respect to HbA1c levels, the frequency of SH was lowest with HbA1c levels 7.0% to 7.5% being higher at levels above or below this range. In addition to T1D duration and HbA1c, SH was more likely to occur in participants who had lower education levels, had lower household income and did not have private insurance ($p<0.001$ for each in multivariate model). Black and Hispanic participants had greater frequency of SH than non-Hispanic whites and pump users had a greater frequency of SH than injection users, but neither was significant in the multivariate model. There was a higher occurrence of ≥1 SH event (17.9% vs. 9.0%, $p<0.001$) in the past 3 months among depressed participants.

SH has also been related to cardiac abnormalities including arrhythmias (2). The specific physiologic effects of hypoglycemia have been reviewed (2-4) and include reduced myocardial perfusion and electrical disturbances such as prolonged QT intervals corrected for heart rate (QTc) and cardiac arrhythmias associated with hypoglycemia (5). It has been suggested that ECG monitoring during controlled daytime hypoglycemia could help assess the risk of nocturnal hypoglycemia on cardiac arrhythmia and the 'dead in bed' syndrome (6). In a recent study in which 21 of the participants had T1D, 23% (50/216) reported SH and all participants (including those with type 2 diabetes) had a 3.4-fold higher 5-year mortality than participants without SH (3). It is therefore important to better understand factors contributing to the increased frequency of SH in older adults, so that appropriate interventions can be designed to prevent or minimize this serious acute diabetes-related complication.

SH, in addition to being a dangerous metabolic emergency, has been proposed to cause chronic complications in T1D. Brain damage from SH is a major concern (7). Repeated episodes have been related to decline in cognitive function in some but not all reports (the DCCT/EDIC study found no association of SH (or treatment group) with decline in cognitive function) (8). Most studies examining cognition following SH did not include older adults with T1D. Fear of hypoglycemia is a well-recognized barrier to achieving optimal glucose control, potentially contributing to the development of microvascular complications (9). While the Eurodiab study did not find an association of baseline SH with incidence of CVD or cross-sectionally with markers of inflammation or endothelial function (10), other studies link hypoglycemia with increased oxidative stress and impaired cardiovascular function (11) and Brownlee and Hirsch hypothesized that increased glycemic variability is an independent risk factor for diabetes-related complications (12).

Poor cognitive function has been associated with increased SH in type 2 diabetes and worse self-care including adherence to diet and exercise (13-15). The relationship between cognitive function and the incidence of SH has not been well-studied in T1D. SH in T1D is more common in the presence of nephropathy and neuropathy, and with the use of nonselective beta blockers and alcohol (16). Hypoglycemic unawareness, which occurs in longer duration diabetes, is another major contributing factor (17). SH is often iatrogenic (18). Errors in insulin administration and difficulty adhering to complicated insulin regimens may be more common in older adults and could be associated with poor numeracy, dexterity, vision, cognition, and/or social support.

Although care of T1D has improved, the incidence and prevalence of T1D continues to increase. Furthermore, the population of adults with T1D and long (>40 years) duration of diabetes continues to rise and presents new challenges for the health care system as indicated by their increased frequency of SH. New studies are required to further investigate the causes of increased SH in this population and what therapeutic interventions best prevent SH.

1.2 Study Objective

The primary objective of the study is to identify factors associated with the occurrence of severe hypoglycemia in older adults with T1D. It is hoped that the study results can be used to design an intervention study with the goal of reducing the incidence of severe hypoglycemia in older adults.

1.3 Study Synopsis

Study Design

The study design will be similar to a case: control approach. Participants will be selected as either a case (SH event in past 12 months) or a control (no SH in past 3 years) to ascertain factors associated with SH.

Case: SH event in past 12 months, defined as an event requiring assistance of another person, as a result of altered consciousness or confusion, to administer carbohydrate, glucagon, or other resuscitative actions.

Control: No SH in past 3 years

Sample Size: 100 cases and 100 controls (frequency matched by clinical site and age)

Testing and Assessments:

- Cognitive Assessments:
  - Montreal Cognitive Assessment
  - Symbol Digit Modalities Test
  - Trail Making Test
  - Hopkins Verbal Learning Test-Revised
- Geriatric Depression Scale
- Diabetes Numeracy Test (shorted version—15 questions)
- Functional Activities Questionnaire
- Grooved Pegboard test
- Vision assessment

- Hypoglycemic Unawareness Assessment –Clarke survey
- Hypoglycemia Fear Survey
- Blood Glucose Attitudes Scale
- Duke Social support scale
- Frailty 10 foot walk
- Blinded continuous glucose monitoring (CGM) for up to 14 days
- Laboratory testing: HbA1c, non-fasting C-peptide, glucose, and creatinine
- Heart activity monitor for up to 14 days for a few participants from selected sites who are willing
- Activity tracker device for up to 14 days for a few participants from selected sites who are willing

1.4 General Considerations

The study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and with the standards of Good Clinical Practice.

CHAPTER 2: ELIGIBILITY CRITERIA AND ENROLLMENT

2.1 Study Population

Participants in the study must meet criteria to be either a case or control as described below.

2.2 Eligibility and Exclusion Criteria

Criteria for Cases and Controls:

Case: SH event in past 12 months, defined as an event requiring assistance of another person, as a result of altered consciousness or confusion, to administer carbohydrate, glucagon, or other resuscitative actions.

Control: No SH in past 3 years

Case and control status will be determined verbally by self-report prior to consent and then documented by a series of questions on the case report forms.

Eligibility and Exclusion Criteria for Cases and Controls:

Eligibility Criteria

1) Clinical diagnosis of presumed autoimmune type 1 diabetes
2) Age ≥60 years old
3) Duration of T1D ≥20 years
4) Insulin presently required
5) Has not used a real-time CGM device for the past 2 weeks
6) Fluent in English

Exclusion Criteria

1) Glomerular filtration rate <30 (based on available data in medical record from usual care; if no results available, then individual is eligible)
2) Diagnosis of dementia that is moderate or advanced
3) Serious illnesses where life expectancy is <1 year
4) History of pancreatic transplant

Eligibility will be assessed as part of usual care.

Control Selection: As much as possible, controls will be frequency matched on clinic and as much as possible in 5-year age group bins.

2.3 Informed Consent

Prior to completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained. Depending on IRB requirements, the consent may be written or verbal.

2.4 T1D Exchange Clinic Registry

If a participant is not already enrolled in the T1D Exchange clinic registry, they will become part of the registry when joining this study. As a registry participant, information from their medical record may be entered into the registry database at least once a year and they will have an opportunity to provide their email address to be contacted in the future about other studies for which they may be eligible.

2.5 T1D Exchange Biobank

The T1D Exchange Biobank is designed to support ongoing and future research by qualified investigators by collecting information and biosamples from people with T1D. Samples will be used only for the study of T1D and its complications. Within this overarching purpose, multiple T1D Exchange studies will collect blood samples specifically for the T1D Exchange Biobank, whose policies and procedures will govern the release of data and samples to investigators. The T1D Exchange Biobank is directed by the Biobank Operations Center at Benaroya Research Institute, Seattle, WA and the Jaeb Center for Health Research (JCHR) who are responsible for the oversight of the operations of this database and biosample repository. Specifically, the JCHR IRB reviews and approves specific protocols under which data and samples may be obtained and shared, and ensures that adequate provisions protect the privacy and confidentiality of participants and data.

Blood will be drawn for the T1D Exchange Biobank during the study blood draw and may include DNA, RNA, peripheral blood mononuclear cells (PBMC), serum and plasma. The maximum blood volume collected will not exceed 250 ml.

CHAPTER 3: STUDY VISITS

Prior to study visits, fingerstick will be performed to ensure the participant is not hypoglycemic at time of assessments. If the participant is hypoglycemic, some of the assessments may be deferred until another visit.

3.1 Visit 1

After informed consent is obtained, the following will be done:

1) Information will be collected from the chart and solicited from the participant with respect to: medications, medical conditions, physical exam, management, demographics, exercise, alcohol consumption, nutrition, insulin use, and other diabetes management factors.
2) Blood will be drawn and sent to the central lab for:
    a. HbA1c
    b. C-peptide (nonfasting) + glucose
    c. Creatinine/GFR
    d. Samples for BioBank storage
3) Testing
    - Montreal Cognitive Assessment
    - Symbol Digit Modalities Test
    - Trail Making Test
    - Hopkins Verbal Learning Test-Revised
    - Grooved Pegboard Test
    - Geriatric Depression Scale
4) CGM sensor (blinded) will be inserted and instructions on calibration, maintenance issues, and removal of the sensor after 7 days will be provided
5) Heart activity monitor may be placed with instructions on how to care for it (optional)
6) Activity tracker monitor may be placed with instructions on how to care for it (optional)

3.2 Visit 2

The second visit will occur 7 to 21 days after the first visit. The following will be done.

1) Testing:
    - Functional Activities Questionnaire
    - Hypoglycemic Unawareness assessment –Clarke survey
    - Hypoglycemia Fear Survey
    - Blood Glucose Attitudes Scale
    - Duke Social Support Index
    - Vision Assessment
    - Diabetes Numeracy Test (DNT 15)
    - Frailty 10 foot walk

2) A new CGM sensor will be inserted

CHAPTER 4: DATA COLLECTION AND TESTING PROCEDURES

4.1 Cognitive Assessments:

4.1.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is an instrument designed to screen for cognitive function (19). MoCA assesses the areas of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. Administration time is approximately 10 minutes.

4.1.2 Symbol Digit Modalities Test

Symbol Digit Modalities Test is a brief test designed to screen participant's motor coordination of speed, learning, visual scanning and overall cognitive functioning (20). This timed assessment asks that specific numbers are pairs with given geometrical figures. Administration time is approximately 5 minutes.

4.1.3 Trail Making Test

The Trail Making Test measures cognitive flexibility, visional search, scanning and speed of processing (20). There are two parts to this timed test. Part A of this test targets all numbers in sequential order and part B of this test connect numbers and letters alternating between the two. Administration time is approximately 4-8 minutes.

4.1.4 Hopkins Verbal Learning Test-Revised

The Hopkins Verbal Learning Test (HVLT-R) is a learning and memory assessment designed with a recall of learned items after a period of time (21). In the test the participant learns and memorizes words in different categories and then is asked to recall those words after a 20-25 minute waiting period. Total administration time, including the delayed recall time is approximately 35 minutes.

4.2 Diabetes Numeracy Test (shorted version—15 questions)

The Diabetes Numeracy Test (DNT-15) is designed to measure numeracy skills in patients with diabetes (22). This test consists of 15 questions in the following areas: nutrition, exercise, blood glucose monitoring, and medication. Math skills are assessed within these categories such as, addition, multiplication or division, fractions, and multi-step mathematics. Administration time is 10-15 minutes.

4.3 Functional Activities Questionnaire

The Functional Activities Questionnaire (FAQ) measures instrumental activities of daily living (IADLs) such as shopping, financial activities and preparing balanced meals (23). The FAQ scale measures 10 domains of functionality. Each item is scored for a level of independence and scores are summed to assess function and possible cognitive impairment. Administration time is approximately 10-15 minutes.

4.4. Grooved Pegboard Test

The Grooved Pegboard Test is a dexterity test that measures performance speed in a fine motor task by examining both sides of the body (24). This test consists of twenty five holes with randomly positioned slots and pegs which have a key along one side. The pegs must be rotated to match the hole before being inserted. Participants are scored based on the length of time in seconds required from start to finish of the test, the number of "drops" a participant makes during the test, and the number of pegs correctly placed in the holes. Administration time is approximately 10 minutes.

4.5 Vision Assessment

Vision will be assessed using a near vision reading card binocularly. Participants will read the card and the smallest line the participant can read will be recorded. Administration time is approximately 5 minutes.

4.6 Duke Social Support Index

The Duke Social Support Index (DSSI) measures the strength of a person's social support network through a 11-item questionnaire (25). The 2 dimensions of social support measured are social interaction and subjective support. Administration time is approximately 10 minutes.

4.7 Frailty 10 foot walk

This test will measure the time it takes for participant to walk 10 feet, to obtain an estimate of frailty. Administration time is approximately 10 minutes (26).

4.8 Geriatric Depression Scale

The Geriatric Depression Scale is a 15-item questionnaire asking participants yes or no questions about how they felt over the past week (27). This scale was designed specifically to identify depression in the elderly. Administration time is approximately 10 minutes.

4.9 Continuous Glucose Monitoring (CGM)

At the first visit, a blinded DexCom CGM sensor will be inserted. The participant will receive instructions on calibration, maintenance, and removal of the sensor after 7 days. A second sensor will be inserted at Visit 2, to be worn for another 7 days. The device will then be returned to the clinic.

4.10 Heart Activity Monitor

Some participants at selected clinical sites will be given the option of wearing a heart activity monitor during the time that the CGM is being worn. Such participants will receive instructions on how to apply and remove the monitor. The participant will wear the device for up to 14 days, simultaneous with the CGM device, and return the heart activity monitor to the clinic. The heart activity monitor will assess the frequency and timing of heart arrhythmias.

4.11 Hypoglycemic Unawareness Assessment –Clarke survey

The Clark method of assessing Hypoglycemic Unawareness consists of 8 questions, which evaluate glycemic threshold for, and symptomatic responses to, hypoglycemia. Administration time is approximately 10 minutes.

4.12 Hypoglycemia Fear Survey

The Hypoglycemia Fear Survey measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes (28). It consists of a 10-item Behavior subscale that measured behaviors involved in avoidance and over-treatment of hypoglycemia and a 13-item Worry subscale that measures anxiety and fear surrounding hypoglycemia, each with a 5-choice Likert response format. Administration time is approximately 10 minutes.

4.13 Blood Glucose Attitudes Scale

The Blood Glucose Attitudes Scale is a pilot survey designed to measure fear of hyperglycemia. This survey consists of 8 items of which the first 5 will be used for scoring. Administration time is approximately 5 minutes.

4.14 Activity Tracker

Some participants at selected clinical sites may be given the option of wearing an activity tracker device during the time that the CGM is being worn. Participants who chose to wear this non-invasive device will receive instructions on how to wear the device. The participant will wear the device for up to 14 days, simultaneous with the CGM device, and return the activity tracker to the clinic. This device will assess physical activity.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Adverse Events and Risks

As this is a non-treatment, non-intervention study, study-related adverse events are unlikely to occur. However, informational study-related adverse events will be collected. The risks of having blood drawn are minimal and include some discomfort or bruising.

There is a low risk for developing a local skin infection at the site of the CGM sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

One additional risk for being part of the study is the unlikely chance that sensitive participant information is viewed by someone outside the research team who is not authorized. However, special efforts are being made to ensure that this does not happen (see section 5.5).

There is a minor risk of local allergies from the patch when wearing the heart activity monitor.

5.2 Benefits of Participation

A participant may not benefit. However, those with prior SH may benefit if factors are identified that are associated with SH. Results of this study will provide important new knowledge that will be generalizable to individuals with T1D. After the study, participants will receive the data from the CGM wear, heart activity monitor and activity tracker device if used, which may be useful for the participant's medical care.

5.3 Participant Reimbursement and Compensation

The study will provide $125 in gift cards to each participant for their time, transportation, and costs incurred from the meter test strips necessary for calibration of the CGM. Participants who wear a heart activity monitor will be provided an additional $25 gift card.

5.4 Study Costs

There are no costs to the participant for study participation. The following will be provided by the study at no charge to the participant:

- Blinded CGM and related supplies (gift card provided for meter test strips)
- Study visits and procedures (blood draw)

5.5 Confidentiality

For security purposes, participants will be assigned an identification number that will be used instead of their name. All data and other information sent to the Jaeb Center for Health Research in Tampa, FL, which serves as the coordinating center for the project, will be identified with this number; no names or identifiable health information will be included. Laboratory specimens will be sent to a central laboratory for the study. In compliance with site-specific HIPAA policies, Jaeb Center will enter into a Data Use Agreement with local study sites.

Study data will be entered on the Coordinating Center's secure website through an SSL encrypted connection. The Coordinating Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with

strong encryption. The study website is password-protected and restricted to users who have been authorized by the Coordinating Center to gain access. No identifiable health information of an enrolled participant will be released by the Coordinating Center.

5.6 Quality Assurance

Training for each of the assessments will be standardized across sites and only certified personnel will be allowed to administer the assessments. This will be validated by signatures and monitored at the coordinating center. Validations and quality control checks on the data entered through the secured study website will be conducted.

CHAPTER 6: STATISTICAL CONSIDERATIONS

The approach to sample size and statistical analyses are summarized below. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

6.1 Sample Size

A sample size of 100 cases and 100 controls, with replacement of any participants who do not complete the study, was selected. With this sample size there will be 90% power to detect differences in proportions of approximately 25%.

6.2 Statistical Analyses

6.2.1 Primary Objective

To identify factors associated with the occurrence of severe hypoglycemia in older adults with T1D.

Analysis:

For each of the below primary measures of interest, logistic regression models will be run to test association of each assessment or lab result with SH case/control status.

1. Sensor Data--Percentage of time < 70 mg/dl and coefficient of variation (CV) of glucose variability
2. Cognitive assessments—scores on Montreal Cognitive Assessment, Symbol Digit Modalities Test, Hopkins Verbal Learning Test-Revised, and Trail Making Test
3. Diabetes Numeracy Test score
4. Functional Activities Questionnaire
5. Grooved Pegboard test
6. Vision assessment
7. Hypoglycemic Unawareness assessment score (Clarke)
8. Hypoglycemia Fear Survey score
9. Blood Glucose Attitudes Scale
10. Duke Social support scale score
11. Frailty 10 foot walk—time it takes to complete walk
12. Geriatric Depression Scale
13. HbA1c value
14. C peptide level
15. Exercise
16. Nutrition and insulin use

Potential confounders to control for:

- BMI
- SES
- Diabetes Duration
- Insulin method
- SMBG

Models will be adjusted for the two frequency matched factors by including age as a covariate and treating site as a random effect.

6.2.2 Secondary Objectives

- To examine the correlation between hypoglycemia and ECG abnormalities.

  Analysis:
  Using a regression model, the association between hypoglycemia and ECG abnormalities will be assessed. ECG abnormalities will be captured by the heart activity monitor and hypoglycemia will be captured by the CGM. The timing of major cardiac episodes will be compared to the timing of hypoglycemic events. Also, the number of major cardiac episodes overall will be compared to the overall percentage of time less than different hypoglycemic thresholds and hypoglycemic variability to see if they are correlated.

  - To assess correlations between physical activity, ECG abnormalities, and hypoglycemia, when possible.

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