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A Introduction

A1 Study Abstract and Background

The prevalence of youth-onset type 2 diabetes (T2D) is on the rise, especially in minority and disadvantaged populations.[1] During the COVID-19 pandemic there was a further increase in youth-onset T2D, likely due to more sedentary behaviors.[2] Family history of diabetes, quality of and access to health care, differences by race/ethnicity in insulin sensitivity, diet quality, and minimal physical activity are some of the risk factors for T2D.[3] Furthermore, T2D in youth has been found to be more aggressive in nature with rapid deterioration in β-cell functioning and high rates of diabetes complications, compared to T2D in adults.[4,5] Given the clinical course of youth-onset T2D and limited treatment options (metformin, insulin or subcutaneous GLP-1 agonist), there is an increasing need for interventions that not only improve glycemic control and reduce insulin resistance, but also promote behavioral modifications such as exercise and healthy eating.

In youth with type 1 diabetes (T1D), the use of continuous glucose monitoring (CGM) has been associated with decreased hemoglobin A1c (HbA1c) levels and increased time in range (TIR), while also improving quality of life[6,7]. Similar trends have been noted in adults with T2D, in which investigators concluded that the real-time glycemic feedback provided by CGM gave way to lifestyle modifications, including more physical activity, that led to improvements in glycemic control.[8,9] The SEARCH study found that most youth with T2D test their glucose levels fewer than 3 times per day[8] and 27% of youth with T2D had poor glycemic control (HbA1c > 9.5%)[10-12].

Given the improvements observed when implementing CGM in youth with T1D and adults with T2D, there is reason to believe that CGM could play a pivotal role in helping youth with T2D check their blood sugars more frequently, while also promoting behavioral modifications that improve glycemic control. There is limited information on the use of CGM in youth with T2D.

We conducted a pilot clinical trial to determine if a complementary 10-day trial of CGM use in youth with T2D impacts glycemic control and behavior.

A2 Primary Hypothesis

We hypothesize that providing sample complementary CGM at the point of care with standardized CGM education will improve glycemic control in pediatric patients with type 2 diabetes.

B Study Objectives

B1 Primary Aim

To determine if 10-day trial CGM use in youth with T2D improves glycemic control (changes in time in range and Hemoglobin A1c).

B2 Secondary Aim

To determine if 10-day trial CGM use in youth with T2D improves measures of diabetes distress and diabetes related quality of life.

C Study Design

C1 Overview of Study Design

This is a hypothesis-driven, pre-registered, prospective cohort study to determine if point of care placement of complementary CGM with standardized CGM education improves glycemic control.

The study will consist of a baseline visit (coincident with routine clinical care) where a complementary trial CGM is placed at the point of care with standardized CGM education. CGM-related apps will be downloaded on the participant's smartphone. Follow-up phone calls will be conducted by the study team at 5-days and 10-days after CGM placement. CGM data will be recorded at the next follow-up visit (if available) and hemoglobin A1c level (performed as part of routine clinical care) recorded.
Surveys will be completed at baseline, 10-days (via email), and at follow-up (3-6months)

C2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Patients with type 2 diabetes for more than 3 months
- Ages 8-21 years
- CGM naive or no CGM use in the 12 months prior to enrollment
- No minimum A1C level required for eligibility.

2.b Exclusion Criteria

- CGM use in the 12 months prior to enrollment
- Participants with T2D not on insulin

2.c Subject Recruitment Plans and Consent Process

Individual(s) responsible for approaching participant(s): Research coordinators

Where and when recruitment will take place:
Participants will be recruited, screened for eligibility, and consented in a private clinic/room to ensure privacy.

Consent process:
Participants will read through the consent form with the research coordinator, have time to review it and ask questions about the study and study procedures.

2.d Randomization Method and Blinding

Not applicable

2.e Risks and Benefits

This study involves no more than minimal medical risk to the participants as use of CGM is considered standard of care per the American Diabetes Association guidelines.

Risks associated with use of CGM may include hypoglycemia (low blood sugar) or hyperglycemia (high blood sugar) in cases where information provided by the CGM device is inaccurate and used to make treatment decisions or where hardware or set-up issues disable alarms and alerts. Patients will be advised to confirm with a fingerstick blood sugar if symptoms do not match CGM readings.

Patients may also experience skin irritation or redness around the CGM device's adhesive patch. The CGM may inadvertently fall off, and if that occurs, the patient will resume checking fingerstick blood sugars as they were previously.

To minimize risk, when the diabetes nurse/CDCES places the CGM, the nurse will perform routine standardized education including setting up alerts. The CGM devices provide blood sugars every 5 minutes (that creates a continuous reading) versus the typical 4-5 fingerstick blood sugars usually checked per day. Therefore, the CGM actually minimizes risk of hypoglycemia by alerting users to impending hypoglycemia which may not have been previously detected. Participants will have been taught signs/symptoms of hypoglycemia per routine new-onset diabetes education. They will be educated to check blood sugar via fingerstick if they have any sign/symptoms of hypoglycemia and treat accordingly. If they do not understand how to use the device, they have access to Pediatric Endocrinology on-call provider and Dexcom customer service for assistance, and device may be removed early. The risk of device malfunction is extremely low.

The CGM will be applied in clinic by diabetes nursing staff. If patient reports any irritation or signs of infection at the site, the CGM will be removed early. If the CGM is removed early either accidentally or intentionally, participants will be offered a replacement CGM. They will have to resume previous blood sugar monitoring with glucometer and fingersticks, as the patient was using prior to placement of CGM.

Confidentiality: There is the risk that psychological, emotional, financial, social, and legal risks might result if confidentiality cannot be maintained in this study. All study team members are HIPPA trained and will take every step to respect participants' privacy and protect their confidentiality throughout the study. We share the information gathered in the study only with the people who need to know this information. All information gathered during this study will be kept in a secure HIPAA compliant database, REDCap.

Benefit: Use of CGM may increase blood sugar monitoring, reduce hypoglycemia, and improve glycemic control.

2.f Early Withdrawal of Subjects

Participants may withdraw from the study at any time by notifying the study team.

2.g When and How to Withdraw Subjects

The participant may choose to withdraw from the study. It will also not impact the course of the participant's clinical care.

2.h Data Collection and Follow-up for Withdrawn Subjects

Data collected from subjects will remain in the dataset, but no follow-up will be conducted on withdrawn subjects.

D Study Procedures

D1 Screening for Eligibility

Patients being seen in the diabetes center will be pre-screened for eligibility by the research team based on the inclusion criteria. Eligibility will be confirmed with the patient's diabetes provider at the time of the clinic visit, and with the potential participant based on the inclusion criteria. The study coordinator will confirm that the participant that they have never used a CGM, or have not used CGM in the prior 12 months and are currently on insulin therapy.

D2 Schedule of Procedures

Eligibility and Consent: If the patient is eligible and interested in the study, the research coordinator will meet with the patient and caregiver in an exam room for privacy and confidentiality. The research coordinator will explain the study and study procedures, read the informed consent form with the participant and caregiver, and allow time for questions on the study and consent form.
If the participant is less than 18 years of age, the parent will sign the consent form and the participant will sign the assent. If the participant is 18 years of age or over, the participant will sign the consent.

At the time of consent, 3 phone numbers are collected from the participant for future follow-up.

At the baseline visit, barriers to prior CGM use or sustained use will be recorded.

The certified diabetes educator (CDCES) will place the CGM and provide standardized education, including education on use of the Dexcom apps, including Dexcom G6 Dexcom Clarity, and Dexcom Follow (optional) for caregivers. The participant's Dexcom Clarity account will be connected to the clinic portal for remote viewing of data.

The nurse/CDCES will follow up with the patient by phone in 5 days (4-6 days if day 5 falls over a weekend) and again at 10 (9-11) days at the end of the CGM session. Assessment and education during these follow-up phone calls will include report of behavior changes related to blood glucose monitoring and insulin administration, and nurse/CDCES recommended dose adjustments based on observed patterns, as well as education on obtaining personal CGM. CGM data (when available) will be recorded.

At the participant's next follow-up visit at 3 months (or up until 6 months if a visit is cancelled), use of personal CGM will be recorded, in addition to Hemoglobin A1c measured at that visit, questions about behavioral changes, and CGM data, if available.

Questionnaires will be administered before and after initiation of the CGM and at their routine diabetes clinic visit 3-months later to assess changes in psychosocial outcomes of diabetes distress and hypoglycemia worry. Surveys will be administered via REDcap survey.

D3 Point of Care CGM Placement and education

Participants will be provided with a Dexcom G6 CGM, which will be placed during the clinic visit by diabetes staff, and CGM education will be provided at the point of care by the nurse/Certified Diabetes Care and Education Specialist (CDCES). Additionally, participants will download apps on their smartphones including Dexcom G6 and Dexcom Clarity. Caregivers and family members will download Dexcom Follow (optional). Education will be provided on using all the apps. Participants' Dexcom Clarity app will be connected to the clinic's Clarity account for remote viewing of data.
Participants without a compatible smartphone will be provided a loaner smartphone for the duration of the 10-day CGM use.

D4 Safety and Adverse Events

4.a Safety and Compliance Monitoring

Site investigators will monitor compliance with the protocol and good clinical practice (GCP) guidelines.

4.b Medical Monitoring for adverse events

Participants will be monitored for adverse events during the study visit, during their CGM wear, and during the follow-up period of up to 6 months.

4.c Definitions of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject.

4.d Classification of Events

- **Relationship**

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

- **Severity**

The severity of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate: Sufficient discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

4.e Data Collection Procedures for Adverse Events

All enrolled participants will be monitored for untoward incidents (e.g., "Adverse Events") occurring during the study. The Principal Investigator (and other designated individuals, if necessary) will conduct regular monitoring for safety concerns and provide general oversight for human subject safety requirements during the study visit and followup period. All adverse events that are anticipated or described in the informed consent form will be logged appropriately and reported to the IRB on at least an annual basis (e.g., at continuing review).

4.f Reporting Procedures

Any Unanticipated Problems or unexpected "Serious Adverse Events" related to the study intervention or in the follow-up period, will be reported to the IRB promptly. Unplanned and non-emergent deviations from the IRB approved protocol will be logged and reported to the IRB annually at continuing review; all planned deviations will be submitted as a Change in Research to the IRB for approval and prior to implementation. All other event reporting requirements will be followed and all necessary parties will be notified of events/problems encountered in the study and/or changes in research, in accordance with all applicable regulations and guidelines.

4.g Adverse Event Reporting Period

Any Unanticipated Problems or unexpected "Serious Adverse Events" related to the study intervention and/or test article and affecting the risk/benefit profile of the study, will be reported to the IRB promptly, and, in all cases, within 10 business days of discovery.

4.h Post-study Adverse Event

Not applicable

E. Statistical Plan

E1. Sample Size Determination and Power

We calculated the sample size to detect a 10% difference in TIR from the first 5-days compared to the second 5 days of CGM wear. Assuming a TIR SD of 18% (20), a 2-sided alpha level of 0.05 and 80% power, a sample size of 28 participants was required. Allowing for 30% attrition, we planned to recruit 40 participants.

E2. Interim Monitoring and Early Stopping

Interim monitoring will be performed by the study team. No early stopping rules planned for this study.

E3. Analysis Plan

Primary outcome variable.
The primary outcomes of the study were change in TIR from the first 5 days compared to the second 5 days of CGM wear, and change in HbA1c level from baseline to follow up at 3-6 months, both assessed with paired *t*-tests.

Secondary outcome variables.
Secondary endpoints included behavioral modification assessed via questions during 5-day and 10-day follow up call. Change in patient-reported outcomes through surveys assessing quality of life and diabetes-distress compared between baseline and follow-up after trial CGM use.

E4. Statistical Methods

Categorical variables will be described using frequencies and percentages. The Shapiro-Wilks test will be used to assess the normality distribution of continuous variables. Normally distributed variables will be described by mean and standard deviation. Non-normally distributed variables will be described by median and interquartile range. Paired t-tests will be used to assess most differences between baseline and follow up. Wilcoxon signed rank tests will be used for the Diabetes Distress Scale scores and sub-scores. Time in range data from the first 5 (± 1) days of CGM wear will be compared to the second 5 (± 1) days for any patients with at least 8+ days of CGM wear. Additional comparisons will be made with the follow-up CGM data recorded at the 3 or 6-month follow-up. Three month follow up data will be used when available. If the 3-month visit is missing, but there is a later 6-month follow-up, the 6-month visit data will be used. Two sample t-tests, and Wilcoxon rank sum tests (for the Diabetes Distress Scale), will be used to assess differences between groups in survey responses. The values $p< 0.05$ are considered statistically significant. Statistical analysis generated using SAS version 9.4

E5. Missing Outcome Data

Dataset will be assessed for missing-ness and noted in results. Statistical tests will be performed to compare groups with and without missing data, to assess for data missing at random.

F. Data Handling and Record Keeping

F1. Confidentiality and Security

All data for this study will be recorded, stored and analyzed in a password-protected file on a HIPAA-compliant and secure drive through Johns Hopkins Medicine, called the SAFE (Secure Analytic Framework Environment) Desktop. This secure environment is provided by JHM and includes productivity software and statistical software. Storing the Data on the SAFE Desktop complies with federal and institutional requirements to protect patient data. Using SAFE reduces the risk of copying data to an unencrypted desktop or device because the SAFE provides the tools to securely analyze and share PHI/PII all within the SAFE environment. Only authorized persons will have access to SAFE Desktop, login and passwords will not be shared and databases will not be left unattended to further minimize risk of loss of confidentiality.

F2. Records Retention

Informed consent documents will be securely stored in a locked file cabinet within a locked office. Informed consents will also be scanned into the participant's electronic medical record. Data will be stored for up to 7 years.

G. Study Administration

G1. Organization and Participating Centers

Johns Hopkins Pediatric Diabetes Center
Mount Washington Pediatric Hospital Diabetes Center

G2. Funding Source

Funding for this study is provided by the Johns Hopkins Children's Center Innovation Award (PI: Wolf) and an investigator initiated research grant from Dexcom, Inc (PI: Wolf)

G3. Subject Stipends or Payments

Participants will receive a $10.00 gift card, and a parking pass at the baseline study visit and a $10.00 gift card at the completed follow-up visit.

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