Feasibility and clinical utility of the Dexcom G6 continuous glucose monitoring device for the care of patients with type 2 diabetes not using insulin therapy.

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Objectives

The primary objective of this study is to evaluate the feasibility and clinical utility of a continuous glucose monitoring device (Dexcom G6) for the care of patients with type 2 diabetes who are on non-insulin therapies. The overarching purpose of the study is to see if the participant's knowledge about their glucose values via the Dexcom alters their health behaviors with respect to eating and exercise. Additionally, this information may improve patient selfperception of well-being and satisfaction with diabetes management.

Background

A continuous glucose monitoring device (CGM), is a medical device that continuously monitors blood sugar in the interstitial fluid of the body. It monitors the blood sugar levels in 1 min or 5 min intervals depending on the device. It is worn anywhere from 10 days to 14 days and can be worn doing any active activity including swimming. Giving the patient a sense of awareness of what their blood sugars range, while eating, exercising, doing everyday activities as well as sleeping. Some devices have low and high alarm settings, so the person can change insulin regimes as needed and avoiding low and high insulin levels. Unfortunately, the CGM's are currently not easily accessible due to cost and the criteria that the Centers for Medicare and Medicaid Services (CMS) have set in order for physician prescriptions for devices to be covered by insurance. Limited data exists regarding the impact of a continuous glucose monitoring (CGM) device on the management of patients with type 2 diabetes (T2D) who are not on insulin therapy. The Dexcom G6 Continuous Glucose Monitoring System (Dexcom G6 System) is a real time, continuous glucose monitoring device FDA approved and indicated for the management of diabetes in persons age 2 years and older, regardless of insulin use.

Inclusion and Exclusion Criteria

	Inclusion Criteria
1.	18-90 years old
2.	Type 2 diabetes of any duration
3.	Hb A1c $\geq$ 7%
4.	BMI $\geq$ 30 kg/m2
5.	Ability to wear CGM (e.g. no dermatological issue precluding device insertion)
6.	Access to a smartphone device
7.	Prior or no prior use of a CGM device (as long as not currently using)

	Exclusion Criteria
1.	Any insulin use in the past 3 months
2.	Planned use of insulin in the next 6 months
3.	Presence of a blood disorder (such as sickle cell anemia) making glycosylated hemoglobin measurement inaccurate
4.	Current use of a weight loss medication
5.	Unable or uncomfortable with wearing a CGM device
6.	Current use of a CGM device.

Rationale for Inclusion criteria: There is no upper limit for Hb A1c for inclusion in this trial. The rationale is to include individuals not using insulin for this study. There is no specific Hb A1c level at which insulin use is mandated or required. Initiation of insulin is dependent on clinician and patient context. If a participant meets clinical indications for insulin initiation by the treating physician, then the participant would not be eligible for the study (as stated explicitly in the exclusion criteria). However, if the treating physician does not think the participant will require insulin in the near future, even when the Hb A1c level is elevated, then the participant would be eligible for the study.

Number of Research Participants

The Dexcom study team plans to enroll up to 60 research participants.

Recruitment Methods

Patients seen in the Center for Integrated and Novel Approaches in Vascular-Metabolic Disease (CINEMA) program will be screened and approached. CINEMA is a patient-centered, teambased intervention for patients with type 2 diabetes or prediabetes at high risk for cardiovascular events, including those with established atherosclerotic cardiovascular disease, elevated coronary artery calcium score >100, chronic heart failure with reduced ejection fraction, and/or chronic kidney disease. The patients in the CINEMA clinical program are an ideal study population for the research objective. The study team is comprised of the treating physicians, nurses, and ancillary personnel of the CINEMA program. The physicians and medical personnel on the study team have prescribed and managed 147 current patients in the clinical CINEMA program with continuous glucose monitoring devices (Dexcom G6 and Freestyle Libre 2 and 3) to date and are well aware of and experienced with the indications, use, and safety of the device/procedure and its complexity. An endocrinologist will also be part of the study team as a consultant if needed. At the time of the patient's clinical visit, the physician, nurse, or dietician on the study team will approach the patient about participation in the study. All research staff will get physician approval prior to discussing the study with potential subjects. Setting Patients will be recruited from the following locations during their CINEMA visit within the University Hospital healthcare system: UH Cleveland Medical Center, UH Chagrin Health Center, UH Westlake Health Center, and UH Twinsburg Health Center.

Consent Process

Physical (face to face) electronic informed consent with an electronic signature will be obtained for all patients prior to participation. The research team will use an iPad that is UH-approved and has access to the REDCap software for electronic informed consenting

Consent will take place in a private location where a study staff member will spend approximately 15 minutes reviewing the goals of the study, inclusion/exclusion criteria, risks and benefits of participation, and procedures involved in participation. Sufficient time will be given to read, comprehend, and understand the goals and procedures of the study. Participants will provide a summary of their role in this research study to the study personnel to ensure complete understanding of the study prior to signing the consent form. After the electronic signature is obtained from both the participant and the study team member reviewing the consent, the patient will receive a copy of the signed consent document. Tablets will be protected with a case that also allows for disinfecting in between volunteers. If in some rare circumstance the tablets do not allow for proper informed consent and electronic signatures, patients will be given a written paper copy to review and sign. The consent will then be uploaded to REDCap for secure storage and privacy. The patient will also be given a paper copy for their records.

Sharing of Results with Research Participants

☒ Results will not be shared with research participants

☒ Results will not be shared with research participants' doctors

As part of clinical care, individual patient data will be provided to the research participants during the unblinded portion of the study, known as Phase 2, which lasts 90 days. The research participant's medical provider will also have access to information collected by the Dexcom G6 continuous glucose monitoring device. Individual results are provided to patients as a part of standard clinical practice and can be accessed directly through their personal electronic device. Summary results of the study outcomes and statistical analysis will not be directly shared with the research participants or their doctors.

Study Design

The investigational device used in this study is the Dexcom G6 Continuous Blood Glucose Monitoring system.

This investigation is a 2-phase cross-over study with patients serving as their own controls. The demographics, medical history, anthropometric and laboratory data are collected from the electronic medical record at baseline for each patient. During Phase 1 (10 days), the patient wears the Dexcom G6 Pro CGM in blinded mode and is unaware and unable to access the CGM data. The patient performs standard care, self-monitoring with twice daily glucose checks using standard finger-sticks and a glucometer device. During this phase, the medical providers are also blinded to the CGM data and continue standard care without any specific intervention. This 10 day phase is meant to establish a

baseline of CGM data including average glucose, time in range, and glucose variability; and is designed to represent the participant's baseline glucose control. As the CGM measures glucose almost continuously, there are thousands of data points during the 10 days to establish a baseline. During Phase 2 (3 months), the patient wears the Dexcom G6 Personal CGM in un-blinded mode and the medical providers have access to the data via Clarity and/or direct download via the transmitter. CGM data are collected continuously in this phase and at the end of the phase. Anthropometric and laboratory data (including Hb A1c) measured as part of routine clinical care (not directly as part of the research) are collected from the electronic medical record at the end of Phase 2. Medical providers are also un-blinded and counsel the patient, in part based on CGM data, as appropriate.

All patients will receive usual care which will include individual and virtual lifestyle education, virtual support group, M.D. visits, medication interventions, referrals to support programs outside the scope of CINEMA program and nursing support.

The primary outcome is change in average glucose (mg/dl) measured by the CGM between Phase 1 and Phase 2. Secondary outcomes include change in time in range (TIR), glucose variability (GV), and glucose management indicator (GMI), measured by CGM, as well as changes in anthropometric, laboratory, medication, and survey data, between Phase 1 and Phase 2, as detailed below in "Data to be collected." As this is a pilot/feasibility study, a formal sample size analysis is not applicable. Nonetheless, we expected 60 participants to be sufficient to observe differences in average glucose between baseline and follow-up given that the baseline data contains ~2500 data points for average glucose during the 10 day phase 1 and the 3 month follow up contains several times that number of data points.

Study Procedures

If the patient agrees to participate in this study, they will be asked to wear the Dexcom G6 Pro in both blinded mode (Phase 1) and unblinded mode (Phase 2). Participants are trained to use the device, including insertion of the sensor, assessing the sensor and device functionality, and data readout during phase 2 by study staff at the baseline (insertion of blinded device) and 10 day visits (return of blinded device and insertion of unblinded device). Trained study personnel provide the participant with step by step instructions as well as documentation and information including the Dexcom Training Trifold, instruction sheets for blinded and unblinded mode, and the Patient Training and Support Document. In Phase 1, which will last 10 days, both the patient and their physician will be unaware and unable to access the results. During Phase 1, the patient will continue regular medical care for glucose monitoring. This includes self-monitoring and twice daily checks using standard finger sticks and a glucometer device. The participant will return after 10 days for a visit to return the blinded CGM device and obtain a new unblinded device. In Phase 2, which lasts 3 months, both the patient and their physician will have access to the continuous monitoring results. If a participant does not have a compatible smartphone device to view the CGM data, then a study smartphone will be provided to the participant for the duration of the study and returned at the end of the study. If the smartphone is damaged, lost, or stolen during the study, the participant will not be responsible for the cost of the device. At the end of the study, the sensor and transmitter are discarded by the participant. The participant may be in contact with the study team and physician at any time. CINEMA is designed to allow realtime patient-provider contact via phone or email with real-time adjustments to medications per standard of care in the clinical program (regardless of research participation). The patient's physician, who is also a study investigator, will be able to adjust medical interventions in Phase 2 based on results from the continuous glucose

monitoring device. During both phases results and data will be stored within a REDCap database. If the patient agrees to participate in the study, information from their medical record and clinic activities will be collected by research staff.

The same provider team caring for the patient in the clinical CINEMA program is the same study team doing the research. Each individual who will be obtaining informed consent is listed on the study team list and several of these same individuals are also clinical staff who will be doing the CGM fitting and de-fitting. Adjustment of medication and other medical recommendations are based on standard of care clinical judgement and practice and is determined in each specific patient situation based on standard of care clinical practice. Patients are followed up in the CINEMA clinical program by the nurse and diabetes educator usually at 1 month after the first visit and then by the MD at 3 months. However, all CINEMA patients may be in contact with the study team and physician at any time, including to report high or low readings and get advice on medical changes needed. CINEMA is designed to allow real-time patient-provider contact via phone or email with real-time adjustments to medications per standard of care in the clinical program (regardless of research participation). Since the study team physician is identical to the patient's personal physician, and the study nurses and diabetes educator are identical to the patient's clinical team, data are available for medical decision making. The CINEMA team uses cloud-based web apps for the CGM devices in clinical use to view data. Both the nurse navigator and certified diabetes educator (study team/clinical care team) monitor the summary data for each CGM device every 2 weeks on a rotating basis. Actionable values are identified either through routine review of the CGM data or when a participant alerts the study team to a value requiring further attention (see description below). If further discussion/attention is needed by a physician, the CINEMA physician (who is both a study member and the patient's clinician) is contacted by phone, email, or pager to address the issue.

A high CGM reading is defined as a blood glucose >180 mg/dl and low is defined as blood glucose <70 mg/dl. When high and low levels are reported by the patient and/or identified by the treating providers (identical to the study team), then medical advice is provided to the patient (as per routine standard clinical practice) to address the high and low values. For example, if a participant is alerted to a mildly low glucose value (<70 mg/dl but >30 mg/dl), the participant is instructed to continue to monitor their blood glucose using the CGM. If a participant is alerted to a lower glucose value (<60 mg/dl) or they have symptoms of hypoglycemia (such as dizziness, lightheadedness, severe fatigue, or sweating), they are instructed to eat something with a starch (e.g., a wheat cracker) or drink a few ounces of fruit juice and recheck their blood glucose with the CGM device. If a participant is alerted to a mild to modestly high glucose value (>180 mg/dl but <300 mg/dl), the participant will be instructed to continue to take current medications as prescribed, avoid eating high glycemic foods, and continue to monitor their blood glucose with the CGM device. If a participant is alerted to severely high glucose value (>300 mg/dl but <500 mg/dl), the participant will be instructed to continue to take current medications as prescribed, avoid eating high glycemic foods, drink 1 to 2 L of water over the next 2 to 4 hours, continue to monitor their blood glucose with the CGM device. If the blood sugar does not decrease to <300 mg/dl over the next 2-4 hours, they may require urgent care, so the participant will be referred for immediate medical attention and instructed to go to the nearest emergency room. Should any participant report very severe hyper- (>500mg/dl) or hypoglycemia (<55 mg/dl that does not improve with the aforementioned home actions) that may require urgent care, the participant will be referred for immediate medical attention and instructed to go to the nearest emergency room. In such a situation, or when a participant requires medical advice related to the management of their type 2 diabetes,

during office hours (8 am – 5 pm weekdays), the participant may contact the CINEMA office by telephone (216-844-1357) or email (CINEMA@UHhospitals.org). For questions about their CGM device they will be instructed to call the Dexcom Care program for technical support (1-888-738-3646). Outside of office hours, the participant will be instructed to call the on-call 24/7 nurse help line (855-846-8773) or 911 if there is a serious emergency. It is not expected that insulin would be needed for a participant during the study since all participants by design are not using insulin at study start.

The Dexcom G6 Pro continuous glucose monitoring device is a device approved by the U.S. Food and Drug Administration (FDA) and will be implemented in the study. It is approved for the management of diabetes in persons age 2 and older regardless of background diabetes therapy (including insulin). In addition to glucose monitoring data collected by the Dexcom G6 Pro CGM, the study personnel will also collect laboratory data, survey data, and medication data. Four types of surveys will be administered throughout the research study: The Picture Your Plate Survey (PYP), Diabetes Distress Scale (DDS), International Physical Activity Questionnaire (IPAQ), and Glucose Monitoring Satisfaction Survey (GMSS). At study Visit 1, the research team will administer the Picture Your Plate Survey, Diabetes Distress Scale, and International Physical Activity Questionnaire. At study Visit 3, the research team will re-administer these surveys in addition to the Glucose Monitoring Satisfaction Survey. Surveys will be completed via pen and paper or iPad. Participants will also be offered the option to take home paper copies of each survey and return them completed at the following study visit. Throughout the research study, medical and laboratory information will also be collected from the patient's electronic medical record.

Study Timeline

The total duration of the study will involve 100 days of collected data for each participant. This includes the Phase 1 (10 days blinded) and Phase 2 (90 days unblinded) portions of the study. A total of three study visits are required for participation. During the patient's clinical visit, a research study member will approach them about study participation. If willing to participate, the patient will spend approximately one hour engaging in research-related activities- including informed consent, DexCom G6 Pro fitting, and completing baseline study questionnaires. The second study visit will occur at the end of Phase 1 and will require approximately 45 minutes for returning the blinded DexCom G6 Pro device, fitting of the unblinded DexCom G6 Pro device, and instructions for using the new CGM device. The final visit will occur at the end of Phase 2 and requires approximately 45 minutes. At this study visit, the participant will return the CGM device and complete the study questionnaires. Usage of the Dexcom G6 CGM will not require additional time beyond normal clinic visitation and fitting. The participant will not be financially responsible for devices that are stolen, broken, or lost. After the study is completed, participants will be eligible for clinical prescription of a CGM.

Data to be Collected

Data collected within this study will include continuous glucose monitoring data, laboratory data, medication data, and survey data, as detailed below.

CGM:

a. Average glucose (mg/dl) – primary outcome
b. Time in range (%)
c. Glucose variability (standard deviation, mg/dl)
d. Glucose management indicator (%)

Laboratory:

a. Hb A1c
b. Total cholesterol
c. LDL-cholesterol
d. HDL-cholesterol
e. Triglycerides
f. Systolic and diastolic blood pressure
g. Body mass index

Medication data:

a. Number of medication changes (add, subtract, dose change)

Survey data:

A total of four surveys will be provided to research participants:

a. The International Physical Activity Questionnaire
b. Glucose Monitoring Satisfaction Survey
c. Picture Your Plate Survey
d. Diabetes Distress Screening Scale

Data Analysis Plan

Baseline characteristics of the study cohort will be reported. Each participant will have one data point with their total average (reported by the CGM device) at baseline, 30 days, 60 days, and 90 days. The primary and secondary outcomes will be analyzed using paired sample t-tests since participants will serve as their own controls. As this is a pilot/feasibility study, a formal sample size analysis is not applicable. Nonetheless, we expected 60 participants to be sufficient to observe differences in average glucose between baseline and follow-up given that the baseline data contains ~2500 data points for average glucose during the 10 day phase 1 and the 3 month follow up contains several times that number of data points.

Risks to Research Participants

Insertion of the sensor wire: Participants in the study will be using the Dexcom G6 continuous glucose monitoring device, which has known risks. There is a chance that a sensor wire could break or detach during insertion, remaining under the skin. While uncommon, insertion of the sensor can cause infection, bleeding, or pain. Previous clinical studies have also shown slight redness and swelling following insertion of the sensor wire.

Adhesive patch: Participants using the Dexcom G6 may experience local skin irritation caused by the device's adhesive patch.

Risks of CGM malfunction/inaccuracy: There may be a risk of relying on the CGM for medical management, as there is a possibility that an incorrect reading or incorrect use of the device could lead to a medical problem. In the event that the CGM device is registering possibly inaccurate readings, we will ask the participant to confirm blood glucose using a fingerstick test (as per current standard of care). If the device is judged to be defective, it will be removed by the participant and a new device will be reinserted (as per current standard of care).

Study Questionnaires: Research participants may experience discomfort while completing questionnaires throughout the study. Participants may skip any questions that they are uncomfortable answering.

Confidentiality: Any time information is collected about you there is a potential risk for breached confidentiality. While this risk is small, it is possible that others improperly access your information. For more information on how the study team will ensure this is a minimal risk please see the data management and confidentiality section.

Provisions to Protect the Privacy Interests of Research Participants

Patients will be approached and consented in a private location, such as inside a patient examination room. At the initial screening session, full detail of the study goals, risks and benefits, and full detail of the study procedures will be provided in written and oral form. Participants will be asked to consent using a mechanism approved by the Institutional Review Board at University Hospitals. Participants will only be enrolled after additional screening is completed for eligibility. It will be made clear to participants that they may withdraw at any time without penalty, and that they may contact the University Hospitals Cleveland Medical Center's Research Subject Rights phone line at (216) 983-4979 if for any reason they believe that their rights regarding privacy or risk to health have been infringed.

To ensure confidentiality, participants will be identified to study investigators by code numbers only. The research team will have identifying information when needed for linkage and for auditing. Data will be password protected on encrypted devices and under the direct supervision of the principal investigator. Patients are also encouraged to utilize personal devices while accessing CGM data obtained by the Dexcom G6. The plan for data and safety monitoring of the research to ensure the safety of participants is described below.

Potential Benefit to Research Participants

There are no direct benefits from participating in this study. However, this information helps improve the knowledge of how to improve patient adherence to diet and physical activity recommendations. In addition, this information will help improve perception of well-being and satisfaction with diabetes management. We hope the information learned from this study will help lead to the development of improved treatment methods and guidelines for use in improving treatment outcomes for these patients. After the study is completed, participants will be eligible for clinical prescription of a CGM.

Withdrawal of Research Participants

Subjects enrolled in the study may voluntarily withdraw at any time without affecting their future medical treatment or benefits. For employees of University Hospitals or students of CWRU, choosing not

to participate or withdrawing from this study will not affect their employment or class standing, nor will the results be shared with their supervisor. In the event of a participant withdrawal, the CGM sensor and transmitter will be removed by the participant and discarded or returned to the study team. If the participant has been provided a reader, it will be returned to the study team.

The data collected from the patient prior to withdrawal from the study will remain part of the database and may not be removed. The study team will ask the patient if standard care data can continue to be collected from their medical record.

Alternatives to Participation

As a voluntary research study, the alternative to participating is choosing not to participate. However, patients may still receive the Dexcom G6 continuous glucose monitor device as part of standard of care. The decision whether or not to participate will in no way influence any care that the patient may receive at University Hospitals, nor will it affect interactions with any research study personnel.

Costs to Research Participants

The cost of usual medical care for procedures, examinations, and medications will continue to be billed to the patient or to their insurance. There will be no additional costs to the patient for participating in the study.

The Dexcom G6 continuous glucose monitoring devices will be supplied by Dexcom, Inc. This includes a Dexcom G6 Pro kit for each of the research participants lasting 10 days (Phase 1) and a Dexcom G6 Personal kit for each participant lasting 3 months (Phase 2).

Research Participant Compensation

Enrolled patients will not be provided incentives or compensation for participating in this research study.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

Throughout the duration of this study, the research personnel will conduct bi-weekly reviews of data collected and protocol adherence to ensure the safety of research participants. A designated medical monitor, PA Caitlyn Omoregie, will review study materials at a minimum of every 6 months to ensure the safety of participants. Materials reviewed will include recruitment logs, adverse events, and protocol deviations occurring throughout the study.

Drugs or Devices

The device used to continuously monitor patient glucose levels is the Dexcom G6. This device includes a sensor, applicator, and transmitter. The single-use sensor is located inside the applicator and obtains glucose information from the patient's abdomen or buttocks. The transmitter captures and stores this data obtained by the sensor. After inserting the sensor, the single-use transmitter is attached to the transmitter holder.

The patient will need to utilize their personal device or a device provided by the study team as a CGM display. This device receives information captured and transmitted by the Dexcom G6. With the Dexcom G6 application on their smartphone, patients can view their glucose data for Phase 2 of the study

(unblinded). The Dexcom G6 app is compatible with both Apple (iPhone and Apple Watch) and Android (Samsung, LG, Google, Motorola, Huawei, and Android Wear Watches) devices. A full list is available here: https://www.dexcom.com/compatibility/dexcomg6-app. A compatible device will be provided to the participant for the duration of the study if the participant does not own a compatible device.