Continuous Glucose Monitor (CGM) Use in COVID-19 Patients

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MAYO CLINIC

General Study Information

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Study Title: Continuous Glucose Monitor (CGM) Use in COVID-19 Patients

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Research Question and Aims

Hypothesis: CGM (continuous glucose monitor) used in the hospital in patients with COVID-19 will be as accurate as POC (point of care) glucose monitors. Provider acknowledgement CGM alarms of rapidly changing glucose trends will prevent episodes of hyper and hypoglycemia. If CGMs are found to be accurate, then their information can be used to monitor glucose level, and POC glucometer check frequency can be safely decreased to limit staff exposure to COVID19 patients and to decrease the use of personal protective equipment.

Aims, purpose, or objectives:
1. To determine if CGMs worn in the non-ICU hospital setting by patients with a diagnosis of COVID-19 and diabetes have adequate accuracy for blood glucose monitoring when compared to point-of-care capillary glucose measurement.
2. To determine if CGM use will decrease the frequency of POC (point of care) glucometer checks done in patients with COVID-19 diagnosis.
3. To determine if alerts given by CGMs worn by patients with diabetes and COVID19 would prevent episodes of hyperglycemia and hypoglycemia.

Background:

Diabetes Mellitus (DM) affects approximately 34.2 million (10.5%) Americans. Hyperglycemia and hypoglycemia in hospitalized patients have been associated with unfavorable clinical outcomes, including higher rates of sepsis, deconditioning, mortality and longer hospital stay. Untreated hypoglycemia may lead to neurological damage, cognitive decline, seizures and coma. Additionally, the management of the diabetic complications doubles the inpatient cost per capita compared to non-diabetic patients.

Currently, the hospital standard of care for glucose monitoring in diabetic patients is POC capillary blood glucose measurement performed usually before meals and at bedtime. This approach however only provides limited glucose measurements throughout the day and fails to detect nocturnal or asymptomatic hypoglycemia or hyperglycemia episodes, all of which are common insulin therapy complications. Continuous Glucose Monitors (CGM), a newly introduced technology, represent an alternative to this standard of care, with the potential to assist making personalized therapy decisions. CGMs measure and record levels of subcutaneous interstitial glucose every 5 minutes. The subcutaneous glucose measured by most recent CGMs closely mirror the capillary blood glucose levels. This continuous monitoring allows for better assessment of nocturnal or asymptomatic hypoglycemia or hyperglycemia, and shows glycemic patterns following treatment interventions. This monitoring allows for timely interventions, and was shown to reduce hyperglycemia and hypoglycemia episodes. Recent studies have demonstrated improved glycemic control in insulin-treated DM patients using

CGM in outpatient setting. FDA has approved these devices in outpatient setting for glucose monitoring and for dosing of insulin injection even without capillary blood glucose confirmation. In the outpatient setting these devices have become standard of care for both type 1 and type 2 diabetes management. Their use in inpatient setting is limited, and at this time it is not FDA approved. Concerns for reading accuracy in case of rapidly fluctuating clinical parameters, hypoxemia, tissue hypoperfusion and IV medications use have prevented the approval of these devices in inpatient setting. Still, when evaluated in hospitalized patients, small studies have found that CGMs are accurate and they can detected more episodes of hypo and hyperglycemia than POC glucometers, especially between meals and at night time.

COVID-19 pandemic has led to increase hospitalization for patients with diabetes mellitus. Current guidelines recommend treatment with high dose of steroids for COVID-19 patients requiring oxygen supplementation. This therapy leads to hyperglycemia in patients with known DM, but also in patients without previous diagnosis of diabetes. Hyperglycemia treated with insulin could lead to hypoglycemic episodes, especially in frail and very sick patients. Close monitoring of blood glucose is imperative in these patients.

The blood glucose monitoring with POC blood glucose monitors is done at bedside by nursing staff. This requires direct contact with the patient and nurse presence in the room. Depending on frequency of glucose monitoring this presence ranges from 4 times per day to every hour if patients are receiving therapy with IV insulin. Patients with COVID-19 require modified airborne isolation and nursing staff has to use PPE when entering patients' rooms.

A few pilot studies had evaluated the use of CGMs in patients with COVID19 with the aim of reducing hypo and hyperglycemia episodes and nursing staff exposure.

Manufacturers (DEXCOM and ABBOTT) are providing CGM sensors and readers to be used in COVID19 patients with the aim of decreasing the use of health care resources (PPEs) and health care providers' effort during the pandemic. Even if these sensors are not approved by FDA to be used in inpatient setting, FDA has allowed manufacturers to provide these devices to be used in COVID19 patients "to allow hospital staff to remotely monitor glucose in patients to reduce patient interaction, limiting viral exposure by hospital staff and preserving PPE."

With this study we aim to determine if CGMs are as accurate as POC glucometers, if CGM alerts can reduce episodes of hypo and hyperglycemia, and if by using CGM data to dose insulin we can decrease the number of finger-sticks and nurse exposure to COVID19 patients.

Study Design and Methods

Methods:

All patients admitted to the hospital in inpatient status with a diagnosis of COVID-19 will be screened and identified by research team. Patients meeting inclusion criteria will be approached by a research team member and will be asked to enroll. The study will be explained and informed consent will be discussed in detail. If patients agree to enroll, they will be fitted with a Dexcom G6 sensor by nursing staff as per protocol. If MRI imaging is planned, sensor placement will be deferred until after MRI is completed. The CGM will not interfere with Xrays or CT scans (sensor can be covered by a lead shield if needed). A hospitalist or IP Endocrinology staff can temporarily remove the transmitter if it will interfere with medical testing.

Diabetes educators and Endocrinology ARNPs will be available to help with the following tasks. The CGM information will be entered into receiver phone and iPad tablet present at nursing station. The receiver phone will be placed outside patient room in nursing alcove. Here it will remain available for staff to use and to respond to CGM alarms. Alarm limits for hypoglycemia and hyperglycemia will be set on the receiver phone

and on the iPad tablet at the nursing station. These alarms settings will vary depending on whether the patient is on IV insulin infusion vs. subcutaneous (SQ) insulin. The number of glucose checks required with these two types of insulin varies significantly and requires separate handling as detailed below.

Two flow-sheet protocols will be made available to nursing staff with instructions on data collection and insulin management: one for IV insulin infusion and one for SQ insulin. Nursing staff will choose the appropriate protocol at the time of CGM placement based on the type of insulin the patient is receiving. If the patient is transitioned from IV insulin to SQ insulin during the course of the study, the research team will be contacted to provide instructions on safe transition from the IV insulin protocol to the SQ insulin protocol. CGM presence will be recorded by nursing in patient chart under LDA (lines, drains, airway) section. CGM state will be monitored daily by nursing team and any evidence of localized side effects (skin lesions, pain, sensor and adhesive breakdown) will be recorded in patient's chart. Nurses will be asked to report these changes to research team. Research team will survey these recordings daily and evaluate the patients and confirm these side effects. Should these local skin reactions meet criteria for discontinuation then the sensor will be removed and patient participation in research will be terminated.

After placement, CGMs will enter the "warm up phase" for 2 hours. During this period no CGM data will be displayed and nursing staff will continue BG monitoring using Point of Care (POC) glucometer per orders. Once warm up is completed, CGMs will transmit data every 5 min to the receiver phone and their data can be recorded. Nursing staff will be asked to record CGM values in patient chart.

The use of CGMs will be divided in 2 phases – "Adjustment Phase" and "Utilization Phase". The instructions for these phases will differ for patients on IV insulin infusion vs. SQ insulin infusion and are described in detail below.

For patients receiving subcutaneous (SQ) Insulin:

Adjustment Phase

During the first 24 hours, sensor accuracy will be assessed. Patients will continue to have their blood glucose checked with POC glucometer concomitant with CGM use. CGM readings will be recorded in chart at the same time as POC glucometer reading is obtained. The glucometer readings and CGM data at the time of glucometer readings will be compared by nursing staff. The CGM readings should not be either 15% higher or 15% lower that the corresponding POC glucometer reading. Should this CGM reading fall outside this range, a second reading will be done within 30 minutes and readings will be compared to reassess accuracy. After the patient has had sensor in place for 24 hours and at least 4 POC glucometer glucose checks have been recorded and compared against CGM values and found to fall within the above range, the research team will be notified to determine if the frequency of POC checks can be safely decreased based on CGM accuracy.

If 2 or more consecutive CGM readings do not correlate with POC glucometer values, the research team will be notified. The research team will evaluate the data and decide if the sensor should be replaced and another 24-hour cycle of adjustment phase re-initiated, or if patient participation should be terminated. Only POC glucometer readings will be used to make decision about insulin dosing and administration during this phase. When charting insulin

administration, nursing staff will manually enter the CGM readings obtained at the time of insulin administration into the chart under the "comments" on the MAR screen.

If 4 comparison points – CGM readings and POC glucometer reading – are deemed accurate (within +/- 15% of each other for all 4 readings), then patient will enter the "Utilization Phase".

Utilization Phase

During this phase, once the research team has confirmed CGM accuracy, POC glucometer AND CMG readings will be used to make decisions about insulin dosing and administration. The use of POC glucometer will be decreased as follows:

1. POC glucometer checks will be reduced from 4 times per day (qAC and QHS) to twice per day before breakfast and at bedtime (qAM and qHS)
2. Subcutaneous insulin dose for breakfast and bedtime will be determined based on POC readings
3. Subcutaneous insulin dose for lunch and dinner will be determined based on CGM readings
4. Nursing staff will continue to record CGM readings at the time of every insulin administration in the chart under the "comments" section on the MAR
5. Nursing staff will compare AM and HS (before breakfast and at bedtime) POC glucometer reading to concomitant CGM reading to ensure readings remain accurate (within +/- 15% of each other). If CGM readings will fall outside this range, nursing will contact the research team for directions. The research team will recommend either to retest the accuracy of the sensor with POC glucometer, or to exchange the CGM sensor and then test the accuracy

The CGM will be set up with alarm limits of 85 for low glucose and 250 for high glucose. If these alarms are triggered, the nursing staff will take measures for these alarms as listed below. Treatment decisions will be made based on the POC glucometer reading as follows:

- For hypoglycemia alarm (BG<85mg/dl), POC glucometer will be used to confirm the glucose level. Measures will be taken to prevent or treat hypoglycemia.
    - If BG is 70-85mg/dl, patient will receive 15 gm of carbohydrates PO ASAP and blood glucose will be re-checked in 30 minutes.
    - If BG is <70, hypoglycemia protocol will be initiated. IV D50 pushes or IM glucagon will be used if patient is obtunded and unable to swallow.
      POC glucose will be re-checked in 15-30 minutes to ensure appropriate correction of hypoglycemia.
- For hyperglycemia (sustained BG>250) for more than 2 hours in a row, nursing staff will contact primary provider or inpatient endocrinology team for insulin dosing recommendations. POC glucose check will be obtained based on provider recommendations. Additional insulin will not be given between meals regardless of sensor reading unless otherwise recommended by attending physician or ARNP provider. Close attention will be given to avoid "insulin stacking phenomenon" and potential hypoglycemic events.

For patients receiving IV Insulin infusion:

Please note that during the entirety of the study while the patient is receiving IV insulin, the ***insulin infusion dose will only be adjusted using the POC BG readings****. CGM data will only be used to monitor BG range and if BG is found to be outside of expected range, the POC glucose will be checked and insulin infusion will be adjusted based on the POC glucometer reading.*

Adjustment Phase

In the "Adjustment Phase", during the first 12 hours, sensor accuracy will be assessed. Patients will continue to have their blood glucose (BG) checked with POC glucometer concomitant with CGM use. Nursing staff will check POC BG every 1 hour for the first 12 hours (as per established IV insulin infusion protocol). CGM readings will be recorded in chart at the same time as POC glucometer reading is obtained. These readings will be entered by nursing staff under the "comments" section of the MAR screen. The glucometer readings and CGM data at the time of glucometer readings will be compared by nursing staff. The CGM readings should not be either 15% higher or 15% lower that the corresponding POC glucometer reading. Should this CGM reading fall outside this range, a second reading will be done within 30 minutes and readings will be compared to reassess accuracy. After the patient has had sensor in place for 12 hours and at least 12 POC glucometer glucose checks have been recorded and compared against CGM values, the research team will be notified to determine if the frequency of POC checks can be safely decreased based on CGM accuracy.

If 12 comparison points – CGM readings and POC glucometer reading – are deemed accurate (within +/- 15% of each other for all 12 readings), then patient will enter the "Utilization Phase".

If 2 or more consecutive CGM readings do not correlate with POC glucometer values, the research team will be notified. The research team will evaluate the data and decide if the sensor should be replaced and another 12-hour cycle of adjustment phase re-initiated or if patient participation should be terminated.

Utilization Phase

Once CGM accuracy has been established in the "Adjustment Phase" above, the frequency of POC glucose checks will be reduced as follows:

1. POC glucometer checks will be reduced to every 2 hours
2. CGM readings will continue to be recorded hourly by nursing staff.
    a. If CGM glucose remains in range (140-180 mg/dl), the same insulin infusion rate will be continued.
    b. If CGM glucose is out of range (<140 or >180) then nursing staff will resume POC glucose check every 1 hour. Insulin infusion will be adjusted as needed per IV insulin infusion protocol using the POC glucometer reading **only.**
3. If IV insulin infusion dose is adjusted, nursing staff will resume POC glucometer checks every 1 hour until the POC glucose remains in range for 2 consecutive readings
4. Once BG remains within range for 2 consecutive POC glucometer readings, POC glucose checks will be again decreased to every 2 hours

5. If the patient is transitioned from IV insulin infusion to SQ insulin, the nursing staff will notify the research staff and will proceed to the SQ insulin protocol above. The alarms will be adjusted as described in the SQ insulin protocol.

The CGM will be set up with alarm limits of **Low Glucose (<140 mg/dl), Urgent Low Glucose (<70) and High Glucose (>180)**. If these alarms are triggered, the nursing staff will perform a STAT POC glucose check to confirm blood glucose (BG) level. Treatment decisions will be made based on the POC glucometer reading as follows:

- For hypoglycemia:
  - If POC BG is between 85-140 mg/dl, hold IV insulin infusion and re-check POC glucose in 30 minutes
  - If POC BG is between 70-84 mg/dl, hold IV insulin and ask patient to take 15gm of carbohydrates PO ASAP and recheck POC glucose level in 30 minutes
  - If POC BG is < 70, apply hypoglycemia protocol. Hold IV insulin. Give IV D50 or IM glucagon to obtunded patients. Give PO carbohydrates to alert, able to swallow patients. Repeat POC glucose level in 15 min. and 30 min.
  - Continue to check POC blood glucose every 1 hour until glucose remains in range (140-180 mg/dl) for 2 consecutive readings.
  - Once BG remains within range for 2 consecutive POC glucometer readings, POC glucose checks will be decreased to every 2 hours
- For hyperglycemia (BG>180):
  - Check glucose level using POC glucometer and adjust IV insulin infusion rate accordingly
  - Continue checking POC glucose every 1 hour until glucose remains in range (140-180 mg/dl) for 2 consecutive readings
  - Once BG remains within range for 2 consecutive POC glucometer readings, POC glucose checks will be decreased to every 2 hours

Methods (continued):

Treatment of the DM and associated complications, dosing of the insulin, change from PO to insulin treatment and back to PO medications during hospitalization or at discharge will be guided by the admitting team with as needed help from the inpatient Endocrinology Consultation Service.

CGM data will be compared with POC blood glucose monitoring obtained in the hospital. Different patient variables (demographics, comorbidities, labs and vitals, administered medications) will be collected from electronic health record and will be evaluated to determine if they would interfere with CGM readings. The accuracy of CGM for glucose measurement in the hospital will be calculated.

At the time of discharge or after discharge patients will be contacted by research team and administered a survey regarding satisfaction with inpatient care and satisfaction with DM care.

Outcomes measured:
CGM accuracy when compared with POC monitors.
CGM accuracy at detection of hypo or hyperglycemia episodes when compared with POC monitors.
Number of CGM alarms and the clinical result of these alarms: nurse notification, treatment of hypo or hyperglycemia episodes, treatment for rapid declining glucose alarms.
Number of POC glucometer checks in the "Adjustment Phase" and in "Utilization Phase" will be recorded.
Hospital outcomes (length of stay, mortality, readmission and mortality at 30 days)
Patient satisfaction with DM management and inpatient care overall.

Criteria for Discontinuation of Individual Participants:
Subjects can decide to discontinue entirely from the study at any time for any reason. This is documented as withdrawal of consent. Subjects can also be discontinued from the study or discontinued from the study treatment due to Investigator decision as detailed below.
1. Withdrawal of consent.
2. At the Investigator's discretion in certain situations such as lack of compliance or serious adverse event. (A single severe hypoglycemic event resulting in seizure or LOC or DKA).
3. 2 or more hypoglycemic events based on CGM readings that do not correlate with standard finger-stick blood glucose monitor readings and decision to remove the sensor.
4. One DKA event or one episode of hyperglycemic, hyperosmolar nonketotic syndrome (HHNS).
5. Skin infection at the site of device insertion that occurs after placement of the device.
6. Skin irritation at the site of device insertion prompting the patient to request removal of the device.
7. Transfer of the patient to the ICU with intubation, shock, placement on ECMO (Extracorporeal membrane oxygenation) or deterioration of medical condition that in the judgment of the principal investigator carries an unacceptable risk for the participant.

Materials:
CGMs (G6 sensors, G6 transmitters and Phone readers) provided and purchased from DEXCOM .
iPad tablets provided by Mayo Clinic IT Department.
DEXCOM G6 app software is preinstalled on phone readers.
DEXCOM Follow app will be installed on iPads present at nursing station.

Personnel:
Diabetes educators and Endocrinology APRN will provide support for nursing staff and perform the tasks listed above.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 20

Subject population (children, adults, groups):

Admitted adult patients with diabetes and hyperglycemia and diagnosed with COVID-19.

Inclusion Criteria:
Patients 18 years or older.
Patients with diagnosis of COVID-19 respiratory infection
Patient with recent positive SARS-COV2 infection and still positive PCR admitted of non-respiratory diagnoses.
Diagnosis of diabetes mellitus type 1 or type 2
Diagnosis of medication (steroid) induced hyperglycemia (persistent glucose more than 180 mg/dl)
Receiving subcutaneous insulin or IV insulin infusion for hyperglycemia (different protocols will be followed depending on type of insulin)

Exclusion Criteria:
Patients in shock
Patients intubated on mechanical ventilation
Patients with ESRD on HD
Patients placed on ECMO
Patients with DKA or HHS
Patients taking hydroxyurea
Patients receiving more than 4g of acetaminophen in 24 hours
Pregnant or nursing female patients
Patients with skin lesions at the application site that may interfere with placement of the sensor
Patients with known allergy to medical grade adhesive
Patients with significant edema which may interfere with finger stick sample
Patients receiving enteral or parenteral nutrition

Biospecimens

No biospecimens will be collected

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power Statement:
This a pilot study to demonstrate feasibility of CGM use in COVID patients and to determine if a subsequent more extensive implementation and studying of this device will be warranted.

Data Analysis Plan:

Data will be described as percentages or means. Pearson $\chi 2$ and Kruskal Wallis tests will be used to compare categorical and continuous variables respectively. Odds ratios, 95% confidence intervals and p-values will be reported for each model. All tests of significance will be 2-sided and the level of statistical significance will be set at p-value < 0.05.

Mean Absolute Relative Differences will be calculated between matched pairs of POC monitors and the closest CGM reading (within 5 minutes of POC). Additionally, level of agreement between the two devices will be examined with Bland-Altman plots, with particular attention focused on detection agreement in range (70-180 g/dl). Poisson or negative binomial regression will be utilized to assess count variables such as number of alarms, nurse notification, and hypo or hyperglycemia events adjusting for patient characteristics. Finally, longitudinal analysis will be conducted to determine differences associated with medications, clinical parameters or diagnosis. Analysis will seek to define if there are any differences between CGM and POC measurement based on these changes.

Endpoints

Primary:
CGM accuracy - mean absolute relative difference (MARD)
The frequency of POC glucometer use in Adjustment and Utilization phase

Secondary:

- CGM accuracy at detection of hypo or hyperglycemia episodes when compared with POC monitors. (MARD for readings <70g/dl, >180g/dl, >250g/dl)
- CGM accuracy for detecting time in range (70-180 g/dl MARD).
- Number of CGM alarms and the clinical result of these alarms: nurse notification, treatment of hypo or hyperglycemia episodes, treatment for rapid declining glucose alarms.
- Time in therapeutic range for glucose as measured by CGM and POC glucose monitor.
- Detection of medications, clinical parameters or diagnoses that would interfere with CGM reading.
- Effect of CGM use on length of hospital stay.

Clinical safety measures:

- Patients with severe hypoglycemia episodes (POC glucose check below 50 mg/dl).
- Patients with DKA or HHS diagnoses after admission and enrollment in the study.
- Number of sensors with failure.
- Number of sensors removed for procedure.
- Number of sensor related skin reaction (contact dermatitis, infection)