Continuous Glucose Monitoring in General Wards for Prevention of Hypoglycemia: Results From the Glucose Telemetry System Pilot Study

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Introduction
Diabetes mellitus (DM) increases the risk of microvascular and macrovascular complications1,2 and is often associated with multiple comorbidities, which can lead to frequent and prolonged hospitalizations.3-6 At least 26% of hospitalized patients have a history of DM, with an additional 12% exhibiting hyperglycemia without a preadmission diagnosis of DM.1 In 2017, the economic impact of hospitalizations by those with DM was near $123 billion.7 Dysglycemia, defined as hyperglycemia, hypoglycemia, and increased glucose variability, has been associated with poor clinical outcomes in the inpatient setting.8 Hyperglycemia can increase risk for prolonged hospitalization, infection, disability after discharge, and death,3,5,9-13 and has been identified as an independent predictor of mortality in those with and without DM.3 More recently increased glucose variability has also been associated with adverse clinical outcomes14 while inpatient hypoglycemia has been linked to higher health-care utilization costs, prolonged length of stay (LOS), higher risk for hospital readmission, and increased mortality.15,18

Previous studies have reported prevalence of hypoglycemia in hospitalized insulin-treated DM patients ranging from 19% to 26%.15,19,20 As these estimates are based on point-of-care (POC) glucose monitoring, true prevalence is likely greater given the infrequency of testing, typically occurring no more than four to six times per day.3 Hospitalized DM patients often do not experience hypoglycemic symptoms due to concurrent medications with sedating properties or acute illness resulting in changes in mental status, or secondary to underlying loss of counterregulatory responses leading to hypoglycemia unawareness.21 Therefore, many patients in the general wards are at risk for undetected hypoglycemia due to prolonged intervals of time when glucose are not monitored. Continuous glucose monitoring (CGM) systems measure interstitial glucose every few minutes and have the potential of significantly reducing time patients are unmonitored. CGM has demonstrated improved glycemic control for type 2 diabetes (DM2) in the outpatient setting.22,23 However, given the limited evidence in the hospital setting, inpatient CGM use remains investigational.

Studies evaluating use of inpatient CGM have primarily been in the intensive care unit (ICU) setting, with a limited number conducted in the non-ICU setting focusing primarily on validating CGM accuracy.24 There is a lack of evidence examining real-time (RT) CGM for hypoglycemia prevention in non-ICU settings. Additionally, current RT-CGM system design is inherently limited for use in the inpatient setting.

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Glucose values sent from the transmitter to the receiving device must remain close to the patient to ensure continuous transmission, therefore would only be viewable at the bedside. This presents a significant practical limitation as providers and nursing staff would have to frequently enter the patient’s room to view glucose values or hear audible alarms. Without readily viewable and accessible glucose data at the nursing station, CGM would be an inefficient method to monitor patients with DM in the inpatient setting.

To overcome this barrier, we developed the “Glucose Telemetry System” (GTS) utilizing the Dexcom G4 Platinum CGM system (Dexcom, San Diego, CA, USA) and Dexcom software on an iPhone and iPad to display CGM glucose values at the nursing station.25 Here we present the results of the pilot study and describe our experience using GTS in the general medicine hospital wards. In addition to proving feasibility, this pilot study most notably provided information to estimate the sample size needed for a large-scale randomized-controlled trial.

**Methods**

This was a single-center, prospective, randomized pilot study conducted at the Baltimore VA Medical Center on the general medicine wards. The study was approved by the University of Maryland Institutional Review Board and the Veteran Affairs Maryland Health Care System Research and Development Committee. Eligible subjects were adult hospitalized patients with DM2, treated with insulin as part of their outpatient diabetes regimen, and had at least one risk factor for inpatient hypoglycemia including advanced age defined as ≥65 years, renal failure, liver failure, cerebrovascular accident, ≥65 years, or systemic infection19,27,28 as well as patients with an episode of hypoglycemia during a recent hospitalization.

Subjects were managed by basal-bolus insulin regimens during their hospitalization. Insulin adjustments for both insulin initiation and titration for subjects in both groups were performed per protocol based on previously published studies.29 Patients on basal-bolus insulin on an outpatient basis were continued on 80% of their TDD, divided equally between basal and nutritional insulin. Patients on basal insulin and oral and/or other non-insulin-based injectable medications were initiated on a weight-based insulin regimen, also equally divided between basal and nutritional insulin. Patients were initiated on 0.4 units/kg TDD insulin when admission blood glucose (BG) <150 mg/dL, 0.5 units/kg when admission BG was 200-400 mg/dL, and 0.3 units/kg when subjects were ≥70 years old or with an admission serum creatinine ≥2.0 mg/dL. Subjects in both groups were also placed on correctional insulin regimens with rapid-acting insulin (supplemental Table 1) and ordered the institution’s hypoglycemia prevention protocol. Insulin doses were adjusted daily, as needed, based on the standard POC BG values [and not CGM sensor glucose (SG) values] glucose values. Titration of basal insulin (glargine) was based on the fasting morning glucose values (supplemental Table 2). Titration of rapid-acting prandial insulin was performed on a daily basis, as needed, and was based on pre-lunch, pre-dinner, and bedtime BG values.

Patients were initially stratified into two groups based on total number of hypoglycemia risk factors (±2 or ±3 risk factors), and then were randomly assigned to monitoring by POC BG alone (blinded group, standard of care) or RT-CGM using GTS in addition to POC BG (unblinded, intervention group). Subjects randomized to standard of care used “blinded” receivers (alarms and receiver displays were turned off) to collect CGM glucometric values. Subjects randomized to the intervention group used an “unblinded” CGM system where glucose values were transmitted to an Apple iPad at the nurse’s station (Figure 1). GTS specifics have been previously described.26,30 In summary, Dexcom G4 Platinum CGM systems, either in blinded or unblinded form, were utilized for all participants.

Nurses were educated on use of CGM devices such as the BG calibration requirements (every 12 hours), when and how to remove sensors and transmitters if required. In the intervention group, distinct audible alarms were set on the iPad, which would trigger when SG values were <85 mg/dL. Nurses were educated to provide at least 10 g of carbohydrates as a preventive action for impending hypoglycemia if low glucose alarm went off. Hyperglycemia audible alarms were also set on the iPad, which would trigger when SG values ≥400. Above this the CGM system is unable to accurately provide glucose measurements. Use of acetaminophen for study subjects was discouraged due to potential interference possibly resulting in falsely higher SG values.

As hypoglycemia in the inpatient setting has been defined as glucose levels <70 mg/dL,13 our primary outcomes included number of hypoglycemic events (defined as CGM SG values <70 mg/dL for at least 15 minutes), hypoglycemia event rate (defined as number of hypoglycemic episodes per patient per day), percentage of time spent hypoglycemic <70 mg/dL, and clinically significant hypoglycemia (<54 mg/dL) on CGM.31 Nocturnal hypoglycemia was defined as hypoglycemia experienced between 10 PM and 6 AM. Time spent with nocturnal hypoglycemia was defined as the proportion of nocturnal time spent <70 mg/dL and <54 mg/dL. Percentage of time spent at various glucose ranges (70-179, ≥180, and 300 mg/dL) were also evaluated. Average glucose values and markers of glucose variability, such as SD and coefficient of variation, were also calculated.14

Descriptive statistics including means and SDs were computed for continuous variables, and counts and proportions were computed for categorical variables. Wilcoxon’s rank sum test was applied to comparing continuous variables between the intervention group and the standard-of-care group. Fisher’s exact test was used to compare categorical
variables between the two groups. Data analysis was carried out using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

**Results**

Overall, 16 subjects met inclusion criteria: 13 completed the study as 3 participants randomized to the intervention group withdrew for reasons related to minor bleeding at sensor site, transfer to ICU, and 1 consent withdrawal. Baseline characteristics are presented in Table 1. Overall mean age was 69.1 ± 8.0 years, subjects were predominantly male (92%), average BMI was 32.0 ± 7.1 kg/m², mean DM2 duration was 20.2 ± 9.7 years, and average baseline A1c was 8.0% ± 1.8%. Eleven subjects (85%) exhibited two or more micro/macrovascular complications, and eight participants (62%) had three or more risk factors for hypoglycemia. There was a nonstatistically significant higher hypoglycemia event rate of 0.20 ± 0.23 in the standard-of-care group compared to 0.07 ± 0.11 in the intervention group ([P = .31], Table 2). There was a higher proportion of patients (57%) in the standard-of-care group who experienced at least one hypoglycemic event compared to the intervention group (33%). A total of six hypoglycemic events occurred in the standard-of-care group vs two in the intervention group. There was a nonstatistically significant higher percentage of time spent in hypoglycemia (< 70 mg/dL) of 2.44% ± 3.86% vs 0.30% ± 0.39%, P = .54, and clinically significant hypoglycemia of 0.29% ± 0.47% vs 0% (P = .19) in the standard-of-care and the intervention group, respectively. Based on the observed hypoglycemia event rate, sample size calculation revealed that 270 patients (135 in each group) would be necessary to meet 80% power with a P-level of <.05.

### Table 1. Characteristics of Participants at Baseline^a^.

|                                | Overall (N = 13) | Intervention (N = 6) | Standard of care (N = 7) |
|--------------------------------|------------------|----------------------|--------------------------|
| Age, years                     | 69.1 (±8.0)      | 70.2 (±6.4)          | 67.9 (±9.6)              |
| Race, N (%)                    |                  |                      |                          |
| Caucasian                      | 4 (31)           | 2 (33)               | 2 (29)                   |
| African American               | 9 (69)           | 4 (67)               | 5 (71)                   |
| Male sex, N (%)                | 12 (92)          | 5 (83)               | 7 (100)                  |
| Weight, kg                     | 100 (±23.5)      | 99.7 (±29.2)         | 100.3 (±17.8)            |
| BMI, kg/m²                     | 32.0 (±7.1)      | 33.1 (±9.3)          | 30.9 (±4.9)              |
| A1c, %                         | 8.0 (±1.8)       | 7.6 (±1.3)           | 8.4 (±2.4)               |
| DM duration, years             | 20.2 (±9.7)      | 22 (±12.9)           | 18.4 (±6.4)              |
| DM medications, N (%)          |                  |                      |                          |
| Basal only                     | 1 (8)            | 1 (17)               | 0                        |
| Basal + oral meds or GLP-1 RA  | 4 (31)           | 1 (17)               | 3 (43)                   |
| Basal + bolus                  | 5 (38)           | 2 (33)               | 3 (43)                   |
| Basal + bolus + oral meds or GLP-1 RA | 3 (23)           | 2 (33)               | 1 (14)                   |
| Risk factors for inpatient hypoglycemia, n (%) |                  |                      |                          |
| ≤ 2                            | 5 (38)           | 2 (33)               | 3 (43)                   |
| ≥ 3                            | 8 (62)           | 4 (67)               | 4 (57)                   |
| DM complications, N (%)        |                  |                      |                          |
| Retinopathy                    | 6 (46)           | 5 (83)               | 1 (14)                   |
| Neuropathy                     | 6 (46)           | 3 (50)               | 3 (43)                   |
| Nephropathy                    | 12 (92)          | 5 (83)               | 7 (100)                  |
| CAD                            | 6 (46)           | 3 (50)               | 3 (43)                   |
| CVA                            | 5 (38)           | 1 (17)               | 4 (57)                   |
| Amputation                     | 1 (8)            | 1 (17)               | 0                        |
| Primary admission diagnosis, N |                  |                      |                          |
| Cardiovascular                 | 1                | 0                    | 1                        |
| Infectious                     | 3                | 3                    | 0                        |
| Nephrology                     | 2                | 1                    | 1                        |
| Pulmonary                      | 3                | 1                    | 2                        |
| Neurology/musculoskeletal      | 2                | 0                    | 2                        |
| Gastroenterology               | 2                | 1                    | 1                        |

^aMean (±SD).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GLP-1 RA, glucagon-like peptide receptor agonists; Intervention, monitored by GTS (glucose telemetry system); N, number; STD, standard; Standard of Care, monitored by point-of-care blood glucose.
There were two noted failures to prevent hypoglycemia in the intervention group, despite GTS. One failure occurred after a patient received prandial insulin and was transferred to radiology for an imaging study. The second failure occurred post dinner due to decreased appetite and poor nutritional intake. Nurse was not able to respond to the low glucose alarm on the iPad due to another patient emergency on the floor that diverted attention. Almost half of the hypoglycemic events occurred overnight, as three participants in the standard-of-care group experienced nocturnal hypoglycemia captured by blinded CGM vs one patient in the intervention group. Mean percentage of time spent with nocturnal hypoglycemia (<70 mg/dL) was 5.06% ± 3.47% in the standard-of-care group and 1.39% in the intervention group (P = .28), and 1.09% ± 1.4% vs 0% for percentage of time spent <54 mg/dL in the standard-of-care and intervention groups.

Table 2. Primary and Secondary Outcomes.

|                        | Intervention (N = 6) | Standard of care (N = 7) | P-value |
|------------------------|----------------------|--------------------------|---------|
| Hypoglycemic events, N | 2                    | 6                        | NR      |
| Nocturnal hypoglycemic events, N | 1                  | 3                        | NR      |
| Hypoglycemia event rate, N episodes/per patient—per day under CGM | 0.07 (±0.1) | 0.20 (±0.23) | .31     |
| ≥1 hypoglycemic event, n (%) | 2 (33.33) | 4 (57.14) | .60     |
| Patients with blood glucose <54 mg/dL, N (%) | 0 (0) | 3 (42.86) | .19     |
| Percent of time spent |                      |                          |         |
| <54 mg/dL              | 0                    | 0.29 (±0.47)             | .19     |
| <70 mg/dL              | 0.30 (±0.39)         | 2.44 (±3.86)             | .54     |
| 70-179 mg/dL           | 64.24 (±14.56)       | 62.31 (±27.80)           | .94     |
| ≥180 mg/dL             | 35.47 (±14.71)       | 35.25 (±29.38)           | .94     |
| >300 mg/dL             | 3.28 (±5.65)         | 5.52 (±12.64)            | 1.00    |
| Percent of nocturnal time spent |                   |                          |         |
| <54 mg/dL              | 0                    | 1.09 (±1.40)             | .24     |
| <70 mg/dL              | 1.39 (±0)            | 5.06 (±3.47)             | .28     |
| Mean glucose, mg/dL    | 168.57 (±22.97)      | 170.54 (±49.68)          | 1.00    |
| SD, mg/dL              | 51.53 (±15.66)       | 44.87 (±8.54)            | .53     |
| CV, %                  | 30.28 (±6.67)        | 27.15 (±5.22)            | .73     |

*Mean (±SD).
Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; Intervention, monitored by GTS (glucose telemetry system); N, number; NR, not reported; Standard of care, monitored by point-of-care blood glucose.
respectively \((P = .24)\). One subject experienced a prolonged nocturnal hypoglycemic episode in the standard-of-care group with 235 minutes of time spent with SG values <70 mg/dL.

Mean glucose and percentage of time spent in hyperglycemia >180 mg/dL were similar between the standard-of-care and intervention groups: 168.57 ± 22.97 mg/dL vs 170.54 ± 49.68 mg/dL \((P = .93)\) and 35.47% vs 35.25% \((P = .10)\). One subject randomized to RT-CGM had SG values ≥400 mg/dL, at which time the hyperglycemia iPad alarm was triggered. This occurred between breakfast and lunch. The subject had already received rapid-acting insulin at the pre-breakfast POC-BG check and was also expected to receive another dose of rapid-acting insulin pre-lunch. Additional correctional insulin was not given by the primary team due to concerns of insulin stacking. Two patients received acetaminophen, one subject received one dose on the first day of the hospital stay, and the second subject received it periodically through the hospital stay. Five sensors were replaced during study duration due to sensor adhesive or patient-related factors or for imaging necessitating removal, as recommended by the manufacturer [ie, magnetic resonance imaging or computerized tomography scans].

Insulin treatment was not different between the two groups. The median TDD of insulin was 0.27 units/kg for the GTS group vs 0.34 units/kg for the standard-of-care group \((P = .20)\). Similarly, median total basal dose was 0.14 units/kg and 0.20 units/kg \((P = .15)\) for the GTS and standard-of-care groups, respectively, where the median total bolus dose was 0.10 units/kg vs 0.22 units/kg \((P = .32)\) between the two groups. During the first day of study participation, the median TDD of insulin was 0.18 units/kg for GTS and 0.25 units/kg for the standard-of-care group \((P = .09)\). Median-first day total basal dose was 0.11 units/kg vs 0.23 units/kg \((P = .05)\), and median-first day total bolus dose was 0.06 units/kg vs 0.09 units/kg \((P = .77)\) in the RT-CGM group vs standard of care, respectively.

Overall the number of POC-BG values obtained were 4.07 in the GTS group and 4.05 in the standard-of-care group. Median LOS was 5 days and 15 hours vs 3 days and 17 hours in the GTS and standard-of-care groups, respectively \((P = .72)\). Median percentage of time that CGM was utilized was 83% in the RT-CGM group vs 94% in the standard-of-care group \((P = .32)\) [blinded CGM].

**Discussion**

We previously reported on the feasibility of successful transmission of CGM values to the nursing station by using GTS. Results from this pilot study suggest a nonstatistically significant trend toward lower hypoglycemia, including nocturnal hypoglycemia, in patients monitored by GTS. This was observed without an increase in hyperglycemia. Based on the observed hypoglycemia event rate, sample size calculation revealed that 270 patients (135 patients in each group) would be necessary to meet 80% power with a \(P\)-level of <.05.

CGM use in the hospital setting is of increasing interest. The ability to have access to significantly more glucose data could be beneficial as it could prevent hypoglycemic and hyperglycemic excursions. Availability of using alarms for hypoglycemia prevention could lead to increased detection and earlier intervention. A 2016 consensus statement suggested potential benefit of CGM in the hospital to improve patient clinical outcomes and reduce hypoglycemia.\(^{32}\) However, CGM systems are FDA approved only for use in ambulatory patients and are considered investigational in the inpatient setting. Continuation of outpatient CGM during inpatient admission may be limited as well as given lack of necessary institutional infrastructure, policies, and protocols to ensure safety of continued use.

Inpatient hypoglycemia can increase risk of LOS, healthcare utilization cost, and mortality.\(^{15-18}\) In addition, profound hypoglycemia can lead to cardiac arrhythmias\(^{33,34}\) and increase risk of neuroglycopenic symptoms.\(^{35,36}\) Nocturnal hypoglycemia is of great concern as the patient’s ability to detect symptoms is impaired while asleep.\(^{37}\) It has been previously published that up to 36% of hypoglycemia occurred overnight in insulin-treated DM2 patients, with one-third of this population experiencing at least one nocturnal hypoglycemic event.\(^{38}\) As inpatient hypoglycemia is associated with poor clinical outcomes, it is important to explore novel methods of inpatient glucose monitoring.

Costs related to CGM devices and supplies are another practical limitation to CGM use in the hospital. However, it is possible that these costs may be offset if there is a demonstrated benefit in reduction of hypoglycemia in the hospital and length of stay, which would thereby reduce health-care utilization costs. Additionally, use of CGM may provide an opportunity to reduce nursing workload given the ability to monitor BG continuously without increasing manpower. Finally, a pragmatic approach of using this technology in those patients identified to be at the greatest risk of inpatient hypoglycemia may be necessary.

In this pilot study, half of the hypoglycemic episodes occurred were overnight. POC glucose testing is usually performed infrequently, at most four to six times per day and rarely overnight. This highlights an important benefit of RT-CGM as it decreases the interval of time glucose are unmonitored, leading to decreased risk of undetected hypoglycemia.

Nursing staff received ongoing technical support as needed by the research team. Despite the GTS intervention, two episodes of hypoglycemia were not prevented. Failures to prevent hypoglycemia in the GTS group reveal practical challenges of inpatient DM management. Examples of challenges include, but are not limited to, inappropriate timing of prandial insulin administration, unplanned decreased PO intake, or unavailability of nursing staff to quickly respond to...
impending hypoglycemia given higher nursing-to-patient ratios in the general medicine wards.

This pilot study suggests that a simple hypoglycemia prevention protocol with GTS can reduce inpatient hypoglycemia. We did not utilize GTS to address hyperglycemic excursions. Successful and safe use of CGM depends on the ability to accurately interpret glucometric data. As rapid directional changes in glucose using CGM are detectable, this can increase risk of misinterpretation and overreaction to SG trends by general hospital staff to address hyperglycemic excursions and could lead to medical errors, secondary to “insulin stacking.” Another limitation of this study includes the inability to mask the intervention to the investigators, medical team, or nursing staff. In theory this could lead to treatment differences between the groups and achievement of better glycemic control in the RT-CGM group. However, this potential treatment bias was minimized by use of a protocol to adjust insulin based only on POC-BG values.

This study adds to the body of literature supporting inpatient CGM and offers preliminary evidence of using an inpatient GTS. However, further large-scale studies are necessary before widespread adoption. We decided to study insulin-treated DM2 patients with known inpatient hypoglycemia risk factors as we believe that this population could benefit most from inpatient CGM. Based on our power calculation, 270 subjects (135 in each group) need to be recruited to detect a statistically significant treatment effect from GTS in the hypoglycemia event rate. However, considering that these calculations were based on a small sample size—number of participants—along with possible large effect sizes, the actual number of subjects that need to be recruited in order to identify a statistically significant difference in the incidence of inpatient hypoglycemia may be very different.

To our knowledge, such a study would be the first prospective randomized-controlled trial evaluating inpatient RT-CGM use for hypoglycemia prevention in the general wards for DM2 patients at high risk for hypoglycemia (NCT02904512). We are utilizing the Dexcom G6 CGM system, which offers additional benefits of easier sensor insertion, longer sensor-life of 10 days, elimination of calibration requirement reducing burden on hospital staff, and lack of interference by acetaminophen, a commonly used medication in the hospital setting.24,32

Conclusion

Results of this promising pilot study suggest that a GTS might be beneficial for DM2 patients admitted to the general wards. We hope that our recently initiated randomized-controlled trial (ClinicalTrials.gov number NCT02904512) will evaluate whether the use of GTS can prevent hypoglycemia in high-risk insulin-treated DM2 hospitalized patients, expanding the use of CGM devices in the inpatient setting.

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Supplemental Material

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