“Inpatient Diabetes Mellitus (DM) Management With Continuous Glucose Monitoring Devices, a Pilot Study.”

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A. Background and Significance:

Several observational studies have shown that uncontrolled hyperglycemia in hospitalized patients in the non-critical care, non-Intensive Care Unit (non-ICU) setting is associated with prolonged length of stay, increased mortality and an increased incidence of infections [1-6]. Randomized clinical trials in both the critical and the non-ICU settings have shown that by improving glucose control there is a decrease in the incidence of infections, length of stay and inpatient health care costs [7-10].

While hyperglycemia has known deleterious effects, profound hypoglycemia can cause neurological damage [11], as well as induce fatal arrhythmias, due to increased counter regulatory hormones, such as catecholamines, especially in patients with preexisting coronary artery disease [12, 13]. Hypoglycemia in the inpatient setting is more common than in the outpatient setting, with prevalence rates among medical and surgical patients ranging between 3-30% [7, 14-17]. Hypoglycemic events in the hospital setting have been associated with increased mortality and prolonged length of stay [18].

Almost all patients with DM (Diabetes Mellitus) monitor their glucose values with Point of Care (POC) blood glucose testing. The accuracy of most handled glucose meters is at the very least “not optimal” and the FDA allows a variance of 20% for meter measurements and 10% for central laboratory measurements as compared to the true blood glucose levels [19]. Continuous glucose monitoring (CGM) systems have evolved as useful devices providing excellent clinical care in patients with DM [19]. These systems detect glucose in subcutaneous interstitial fluid using a glucose sensor that transmits glucose measurements to a receiving device that reads out average glucose levels every 5 minutes. Using traditional glucose monitors, gaps occur during which time glucose excursions are undetected/ undocumented. CGM provides glucose measures during these time gaps. CGM devices have been shown to improve glycemic control and decrease duration of hypoglycemia in outpatients with DM. CGM are recommended in patients with DM (outpatient setting) with hypoglycemic unawareness, as a declining glucose trend can trigger hypoglycemia-threshold alarms to alert the patient prior to the onset of severe hypoglycemia [20].

Several published studies have examined the use of CGMs in the inpatient setting [21-30]. Most of the studies have been performed in the ICU setting [21-28], where CGM use may not be beneficial to the patients, as patients are monitored closely, with glucose values checked every 1 hour or even more frequently. In the non-ICU setting, where the majority of patients are hospitalized (General Wards), the data for using CGM are limited. In a single arm observational study Burt and colleagues showed that CGM was able to detect for hyperglycemia excursions and more hypoglycemia events than POC-FSBG [29]. In a study that examined the use of CGM in hospitalized patients with DM2 [30], CGM use was able to detect more hypoglycemic events (55 vs 12, $p=0.0001$) compared to the group that was managed with POC-FSBG. 26.3% of the hypoglycemic events were asymptomatic and the majority of these events were identified by CGM use (86.7%). CGM use was more likely to detect nocturnal and daytime hypoglycemic events ($p=0.0399$ and 0.0066 respectively). Notably participants in this clinical trial [30] were insulin naïve (not previously on insulin) DM2 subjects, a group of patients that may not be at

high risk for hypoglycemia. Both of these studies [29, 30] showed that CGM use can detect more hypoglycemic events. However, as these studies were blinded for both investigators and patients, interventions to prevent hypoglycemia were not performed. The next reasonable step is to examine whether CGM use can prevent hypoglycemic events.

In this pilot study we propose to examine the clinical use of CGM in hospitalized insulin treated patients with DM2, admitted in General Medicine Wards setting who are at higher risk for hypoglycemia. We anticipate that our intervention will decrease the number of hypoglycemic events, which represents a significant safety concern in the inpatient setting. We also anticipate that our intervention may decrease hyperglycemia (mild or severe) and therefore may improve clinical outcomes such as nosocomial complications and length of stay. This pilot study may lead us to obtain preliminary data that will help us to design larger clinical studies

B. Aims:

In this randomized clinical trial, we will evaluate whether inpatient use of CGM devices are beneficial in subjects with DM2 in the non-critical care setting (general wards).

Groups:

Half of the hospitalized patients will be monitored with POC testing and non blinded CGM (for both the investigators and the subjects, **Intervention Group**). Management of this group of patients will be based on glucose values obtained by CGM and POC testing.

Half of the subjects will be monitored by POC testing only. CGM results will be blinded (for both the investigators and the subjects, **Control Group**). Management of this group of patients will be based on glucose values obtained by POC-FSBG only.

Aim 1: To determine if we can prevent more hypoglycemic values/ events in the Intervention Group vs Control group.

Hypothesis 1: CGM use (un-blinded) and POC-FSBG will prevent more hypoglycemic values/events compared to subjects that we will be managed by POC-FSBG only.

Aim 2: To determine if subjects that are in the Intervention Group will have decreased hyperglycemia compared to control Group.

Hypothesis 2: Subjects that will be managed by CGM and POC-FSBG will have decreased hyperglycemia compared to subjects that will be managed by POC-FSBG only.

Aim 3: To determine if subjects that are in the Intervention Group will have decreased severe hyperglycemia compared to control Group.

Hypothesis 3: Subjects that will be managed by CGM and POC-FSBG will have decreased severe hyperglycemia compared to subjects that will be managed by POC-FSBG only.

C. Design and Methods:

Human Subjects

Inclusion criteria: ≥21 years of age; history of type 2 DM managed with insulin (either basal bolus, basal with per os DM medications) who also fulfill 1 or more of the following criteria, all known risk factors of hypoglycemia [31-34]: Insulin use of more than 0.6 u/kg, age ≥65, BMI ≤ 27, renal failure, liver failure, active malignancy, congestive heart failure, CVA or sepsis. We will also include hospitalized individuals with type 2 DM treated with insulin that developed a significant hypoglycemic episode in a recent (<6 months) hospitalization.

Exclusion criteria: Subjects that have a history of type 1 DM. History of type 2 DM that are being treated with diet or any combination of oral antidiabetic drugs only, as these patients are less likely to benefit from CGM use. We will also exclude subjects that have significant hyperglycemia or DKA that requires treatment with intravenous insulin infusion and any patients that need hospitalization in the critical care (ICU) setting. Pregnant patients, patients receiving glucorticoids in doses (equivalent) to ≥ 20 mg of hydrocortisone/day, or patients that are expected to require a hospital stay <3 days will also be excluded [35]. Finally, we will exclude any individual with a mental condition rendering the subject incapable of understanding the objectives and potential consequences of the study.

The ethics committee of the University of Maryland and VABMC will approve the study protocol. Informed consent will be obtained from all enrolled subjects.

Lab Values and Glucose Measurements:

All participants will have an Hba1c, CBC and BMP at the time of enrollment in the study, lab values that represent standard of care in admitted subjects with DM.

For DM subjects monitored with POC-FSBG and CGM (**Intervention Group**) or with POC-FSBG only (**Control Group**): In both groups, participants will have their glucose values monitored with POC-FSBG as follows: Pre-breakfast (fasting), pre-lunch, pre-dinner, at bedtime and at 3am) [6, 36]. For admitted veterans that are not eating or that receive continuous enteral nutrition, we will check POC-FSBG every 6 hours [15].

For DM subjects enrolled in the POC-FSBG and CGM (**Intervention Group**), in addition to POC-FSBG, glucose values will be monitored continuously, over 24 hours, by CGM.

POC-FSBG will be measured any time the CGM alarms. In addition POC-FSBG will be measured any time a participant (in either group) develops symptoms that are suggestive of hypoglycemia.

Insulin Treatment:

Titration of insulin will be not made based on the CGM values. Titration adjustments of the insulin regimen will be made by the inpatient diabetes management service team, based on POC-FSBG values. Titration of basal insulin (glargine) will be made based on the fasting am glucose values, based on the following algorithm (**Table 1**).

Table 1. Titration of basal insulin (glargine) [35]	
Fasting am BG values	**Basal dose (IGla) adjustments**
If BG< 60 mg/dl	Decrease dose by 20%
If BG 60-79 mg/dl	Decrease dose by 10%
If BG 80-139 mg/dl	No change
If BG 140-179 mg/dl	Increase dose by 10%
If BG 180-249 mg/dl	Increase dose by 20%
If BG >250 mg/dl	Increase dose by 30%

Titration of correctional (sliding scale) insulin will be adjusted daily based on fasting and pre-meals capillary BG levels (**Table 2**) [35]. If subjects are placed NPO, capillary blood glucose values will be checked every 6 hours and insulin will be administered based on the same insulin algorithm (**Table 2**). Subjects will be treated initially with the "insulin sensitive" regimen, as this group of individuals has a high risk for hypoglycemia. If capillary BG is persistently above 140 mg/dl throughout the day in the absence of hypoglycemia, we will increase the insulin scale regimen from the "insulin sensitive" to the usual or from the "usual" to the "insulin resistant" regimen [15, 35]. If a research subject has POC-FSBG <80 mg/dl, we will decrease accordingly the insulin scale regimen from "insulin resistant" to "usual" or from "usual" to "insulin sensitive" [15, 35].

Table 2. Titration of Correctional (Sliding Scale) Insulin (Novolog) [35].			
BG Values	Insulin sensitive	Usual	Insulin resistant
<80 mg/dl	-1	-1	-2
80-139 mg/dl	0	0	0
140-159 mg/dl	0	+1	+1
160-199 mg/dl	+1	+1	+2
200-249 mg/dl	+2	+3	+4
250-299 mg/dl	+3	+5	+7
300-349 mg/dl	+4	+7	+10
>350 mg/dl	+5	+8	+12

Titration of short acting prandial insulin will be based on pre-lunch, pre-dinner and bedtime BG, adjusting the previous administrated prandial insulin dose, targeting BG values 140-180 mg/dl. If BG is 181-250 mg/dl we will increase the prandial dose by 15%, if it is 251-300 by 20% and if BG was greater than 300 mg/dl we will increase by 30%.

GGM alarm settings and Prevention of Hypoglycemia:

CGM alarms will be set to <85 mg/dl (for prevention for low blood glucose levels) and >400 mg/dl (for alarming for high blood glucose levels). If CGM alarms for low glucose values, a POC-FSBG will be obtained. If it is the POC-FSBG is between 70-85 mg/dl, at least 10 gr of carbohydrates will be given to the subject as a preventive measurement for hypoglycemia. An additional POC-FSBG will be obtained in 15 min in order to confirm that the BG are rising. Similarly, the group of patients that are managed by POC-FSBG only **(Control Group),** if a POC-FSBG will be found to be between 70-85 mg/dl, at least 10 gr of carbohydrates will be given to the subject as a preventive measurement for hypoglycemia.

Treatment of Hypoglycemia

Treatment of hypoglycemia will be similar in the 2 groups and will be based on standard hospital protocols.

Outcome Measures

Aim 1: Hypoglycemic values will be defined as POC-FSBG<70 mg/dl and will be classified as severe if it involved loss of consciousness and/or seizures [35] We will evaluate if there is a difference in the total number of hypoglycemic events between the 2 groups, by evaluating POC BG values. Time spent during hypoglycemia will be also calculated in both groups, using data from GCM devises.

Aim 2: We will compare time spent in hyperglycemia (>180 mg/dl) between the 2 groups. We will compare glucose values obtained from the CGM devises from Interventional group (un-blinded) and Control group (blinded).

Aim 3: We will compare time spent in severe hyperglycemia (>300 mg/dl) between the 2 groups. We will compare glucose values obtained from the CGM devises from Interventional group (un-blinded) and Control group (blinded).

Statistical plan

Descriptive statistics including means and SDs will be computed for continuous variables, and counts and proportions will be computed for categorical variables. Wilcoxon's rank sum test will be applied to comparing continuous variables between the intervention group and the standard-of-care group. Fisher's exact test will be used to compare categorical variables between the two groups. Data analysis will be carried out using SAS statistical program.

Safety

All subjects that participate in the proposed study will be patients with DM that will be admitted to the VABMC hospital for medical reasons. Glucose monitoring for **Control group** will be made with POC-FSBG testing that represents standard of care. **Interventional group** will be monitored as above, however additionally CGM will be utilized. To address any daytime or overnight problems the PI will be on call. The PI is well versed in trouble shooting problems with the CGM devices. Nurses and house staff will receive additional training for the CGM devices.

There are some functional limitations with regard to using CGM in the non-critical care unit. As it is recommended, CGM devices will be removed during MRI or CT scanning. Calibration of CGM devices will be performed every 12 hours, as recommended. As CGM receivers with be used with multiple patients, the devices will be disinfected as recommended with Cavicide before and after use with each patient to prevent transmission of infectious agents. We are familiar with disinfection of CGM receivers, as we frequently use CGM devices in the VABMC DM outpatient clinic, in different patients.

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