

ORIGINAL ARTICLE

Blood glucose control using a computer-guided glucose management system in allogeneic hematopoietic cell transplant recipients

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Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for patients with hematological malignancies. However, is associated with substantial rates of morbidity and mortality. We and others have shown that malglycemia is associated with adverse transplant outcome. Therefore, improving glycemic control may improve transplant outcome. In this prospective study we evaluated the feasibility of using Glucommander (a Computer-Guided Glucose Management System; CGGM) in order to achieve improved glucose control in hospitalized HCT patients. Nineteen adult patients contributed 21 separate instances on CGGM. Patients were on CGGM for a median of 43 h. Median initial blood glucose (BG) on CGGM was 244 mg/dL, and patients on 20 study instances reached the study BG target of 100–140 mg/dL after a median of 6 h. After BG reached the target range, the median average BG level per patient was 124 mg/dL. Six patients had a total of 10 events of BG < 70 mg/dL (0.9% of BG measurements), and no patients experienced BG level < 40 mg/dL. The total estimated duration of BG < 70 mg/dL was 3 h (0.2% of the total CGGM time). In conclusion, our study demonstrates that stringent BG control in HCT patients using CGGM is feasible.

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INTRODUCTION

Hyperglycemia is associated with an increased risk of death among patients with both chronic and acute illnesses.^{1–3} Recently, efforts have been made to control hyperglycemia during hospitalization, but results from clinical trials and retrospective analyses have demonstrated inconsistent outcomes associated with intensive insulin therapy.^{4–9,10–12} There is also evidence that severe hypoglycemia (glucose < 40 mg/dL) in hospitalized patients may have a detrimental effect on outcomes, including cardiac arrest, seizures, hypoglycemia-induced coma and mortality,^{5,13–17} thus limiting the efforts for meticulous glucose control in the hospital. In addition, recent evidence also suggests that glucose variability can be detrimental and increase mortality risk in hospitalized patients.^{18–21}

Allogeneic hematopoietic cell transplantation (HCT) is the only potential curative treatment for patients with high-risk hematological malignancies. However, HCT continues to be associated with substantial rates of non-relapse mortality (NRM) (3-year NRM of 20–30%).^{22,23} Our team has previously shown that malglycemia (hyperglycemia, hypoglycemia or increased glycemic variability) was associated with increased day–200 NRM, overall mortality and infection rate. Our earlier study demonstrated that glucose values above 200 mg/dL were associated with twofold or more increase in NRM, compared with BG values between 101 and 150 mg/dL.²⁴ Similarly, Fuji *et al.*²⁵ demonstrated an association between hyperglycemia and increased risk of organ dysfunction, grade II–IV acute GvHD and NRM in adult patients treated by myeloablative allogeneic HCT, and Gebremedhin *et al.*²⁶ demonstrated that severe hyperglycemia immediately after allogeneic HCT was

predictive of acute GvHD. There is, therefore, interest in improving glycemic control in the hope of improving transplant outcome. Fuji *et al.* previously conducted an intensive glucose control study after HCT. Although the result was feasible, glucose control in that study was still unsatisfactory.²⁷ Computer-Guided Glucose Management (CGGM) may be a mechanism through which intensive glucose control can be attained. In this prospective study we evaluated the feasibility of using *Glucommander* 1.0 (an FDA (Food and Drug Administration)-cleared CGGM) in order to achieve improved glucose control in hospitalized HCT patients. Based on the findings of our prior study²⁴ the primary objective of this study was to examine the ability of CGGM algorithm to control glucose level within target range of 100–140 mg/dL.

SUBJECTS AND METHODS

Patients

Patients 18 years of age and older who underwent allogeneic HCT at the FHCRC (Fred Hutchinson Cancer Research Center), Seattle, and required insulin therapy due to known history of type 2 diabetes, two episodes of blood glucose (BG) level above 180 mg/dL or one BG level above 250 mg/dL were eligible for the study. Exclusion criteria for participation were critically ill patients (Intensive Care Unit status), terminally ill patients, Eastern Cooperative Oncology Group > 3 and diagnosis of type 1 diabetes mellitus. The study received approval by the FHCRC Institutional Review Board.

Nineteen adult patients were treated on the study. Two of those patients were treated on the study during two separate hospitalizations, resulting in a total of 21 separate instances on CGGM.

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Table 1. Patient characteristics

Characteristic	N (%) or median (range)
Number of patients	19
Number of study instances	21
Male patients ^a	13 (68%)
Male instances	15 (71%)
Age at enrollment (years)	52 (22–73)
Days from hematopoietic cell transplantation to enrollment	67 (8–479)
BMI (kg/m ²)	29 (19–41)
<i>Diagnosis^a</i>	
AML	8 (42%)
ALL	4 (21%)
MDS	3 (16%)
NHL	2 (11%)
CML	1 (5%)
HL	1 (5%)
<i>Donor type^a</i>	
Related allo	7 (37%)
URD	12 (63%)
<i>Conditioning^a</i>	
Ablative	14 (74%)
Nonablative	5 (26%)
Prior T2DM	3 (14%)
GvHD prior to enrollment	18 (86%)
Steroids (prednisone)	19 (90%)
Daily prednisone dose at enrollment (mg)	140 (10–200)
Total parenteral nutrition	10 (48%)

Abbreviations: BMI = body mass index; HL = Hodgkin lymphoma; MDS = myelodysplastic syndrome; NHL = non Hodgkin lymphoma; T2DM = type 2 diabetes; URD = unrelated donor.

^aIndicates percent calculated out of 19 patients; otherwise percent calculated out of 21 CGGM instances.

BG monitoring and insulin treatment

BG measurements were obtained by bedside capillary glucose finger stick or venous whole blood, using *Roche Accu-Chek Inform* glucose meter. Insulin was given as continuous IV infusion. BG levels were entered manually into the *Glucommander* Software, which calculated the insulin dose for the next period, and calculated the time for the next BG measurement. Changes to the insulin infusion doses were made manually by the nursing staff, according to the *Glucommander* software recommendations.

Glucommander Software

Glucommander (Glytec, Waltham, MA, USA) is an FDA-cleared CGGM system.²⁸ Using a physician-selected glucose target range and a weight-based multiplier, the computer-based algorithm calculates and recommends an insulin infusion rate and interval to next BG measurement. To initiate the system a desired BG target, patient's weight and BG value are manually entered by a health-care provider, and the initial insulin infusion rate and the time for the next BG measurement are calculated by the software. The interval for BG measurements is between 20 and 120 min based on the rate of glucose level change. The interval of BG checks recommended by *Glucommander* is consistent with the standard of care for insulin infusion, typically every 60 min. Interval is extended to every 120 min if patient is within target range for a specified time, or shortened to every 20 min based on the rate of change of BG level. The system continues recommending the IV insulin infusion rate until discontinued by the health-care provider.

Statistical analysis

Box and whisker plots were used to summarize times to and in different BG ranges as well as the average BG while in those ranges. The box's vertical lines represent quartiles and the whiskers extend to the furthest data point within 1.5 times the inner quartile range. Times to the specified BG range

were calculated as the number of hours from initiation of CGGM to the first measurement within that range. Times in the BG ranges were calculated by assuming a linear relationship between any two values and imputing the time a threshold was crossed. Two of the 19 study participants contributed two separate instances on CGGM, their data were treated as independent for these descriptive analyses, resulting in 21 separate study instances. Simple linear regression and LOESS smoothing were used to highlight trends in the data. Analyses were completed with the statistical computing language R v3.2.2²⁹ and the ggplot2 graphics package v1.0.1.³⁰

RESULTS

Patient characteristics

Nineteen adult patients (13 male), contributed 21 separate instances on CGGM at a median of 69 days (range, 9–481 days) after allogeneic HCT. Median age at study enrollment was 52 years (range, 22–73 years). Patients on 19 of the 21 study instances were on systemic steroids for treatment of GvHD ($n=18$) or diffuse alveolar hemorrhage ($n=1$), with median daily prednisone dose of 140 mg (range, 10–200 mg). Patients on six study instances had documented active infection. Total parental nutrition was given to patients on 10 out of 21 study instances. Three patients had a prior history of type 2 diabetes. Characteristics of patients are presented in Table 1.

Patients remained on CGGM for a median of 43 h (range, 10–195 h) for a total of 1272 h. Patients were removed from CGGM due to: transition from IV insulin to SC insulin ($n=9$), patient request ($n=5$), discharge ($n=4$), other ($n=3$).

Glucose control

Median BG at initiation of CGGM, defined as the first BG reading while on CGGM, was 244 mg/dL (range, 124–421). Patients on 20 of the 21 study instances reached the study BG target of 100–140 mg/dL after a median of 6 h (range, 0–16.2 h) (Figure 1a). There was one instance where the initial BG on CGGM was within 100–140 mg/dL range, as the patient was on standard insulin therapy prior to initiation of CGGM. Thus, for this patient, it took zero hours to reach the target range. The one patient who did not reach the study BG target (study instance no. 21, Figure 4) entered the CGGM with BG level of 421 mg/dL, reached a BG level of 157 mg/dL, and was removed from study after 11.5 h due to patient request. After BG reached the study target range (100–140 mg/dL), the median average BG level per patient was 124 mg/dL (range of 118–167). All patients reached a conventional BG range of 80–180 mg/dL at a median time of 3.8 h (range, 0–10.5 h) (Figure 1a).

Patients had wide variability in glucose level before and after CGGM, while maintaining targeted BG level (100–140 mg/dL) in 61% of the time while on CGGM (Figure 2). For comparison, patients were within target range only 0.58% of the time during the last 24 h prior to initiation of CGGM and 20.95% of the time in the 24 h after completion of CGGM.

After reaching the target range, patients spent a median of 3.8 h under 100 mg/dL and 10.2 h over 140 mg/dL, compared with 26.2 h within the 100–140 mg/dL range (Figure 1b). Stringent glucose control (100–140 mg/dL) was achieved with only 10 documented hypoglycemic episodes (BG < 70 mg/dL; range, 51–67 mg/dL) (0.9% of BG measurements), experienced by six patients (Figure 1c). All six patients who developed hypoglycemia had GvHD and were treated with systemic glucocorticoids at an average dose of 105 mg/day and three patients also had active infections. With the limitation of timing of bedside BG measurements by nursing staff, the estimated median duration of hypoglycemic episodes was 17 min (range, 6–36 min). The total estimated duration of BG < 70 mg/dL for the entire study cohort was 3 h (0.2% of the total time patients were monitored on CGGM) (Figure 1c). No severe hypoglycemic episodes (BG < 40 mg/dL) were detected.

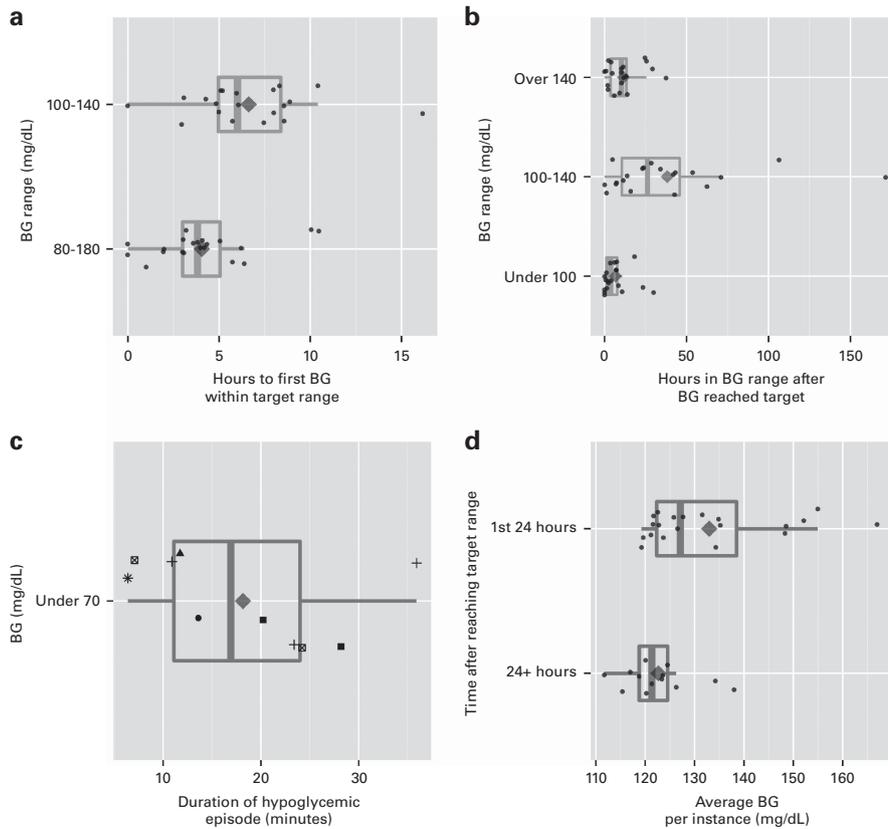


Figure 1. Blood glucose control on CGGM. Box and whisker plots were used to summarize times *to* and *in* different BG ranges as well as the average BG while in those ranges. The box's vertical lines represent quartiles and the whiskers extend to the furthest data point within 1.5 times the inner quartile range. Each black dot represents a study instance, where the distribution along the Y axis is randomized for visualization purposes. Points beyond the whiskers are considered outliers. The diamond represents the sample mean. **(a)** Time to patient's first BG measurement within target range. X axis—hours after initiation of CGGM. Upper graph—time to reach the study stringent BG target of 100–140 mg/dL. Lower graph—time to reach conventional BG level of 80–180 mg/dL. **(b)** After reaching the BG target of 100–140 mg/dL, times above, in and below this range. **(c)** Hypoglycemic episodes (BG 40–70). Each symbol represents a hypoglycemic episode (range, 51–67 mg/dL). Matching symbols indicate the same patient. X axis—length of each hypoglycemic episode. **(d)** Average BG level per patient in the first 24 h after reaching target range (100–140 mg/dL) (upper plot) versus later (lower plot).

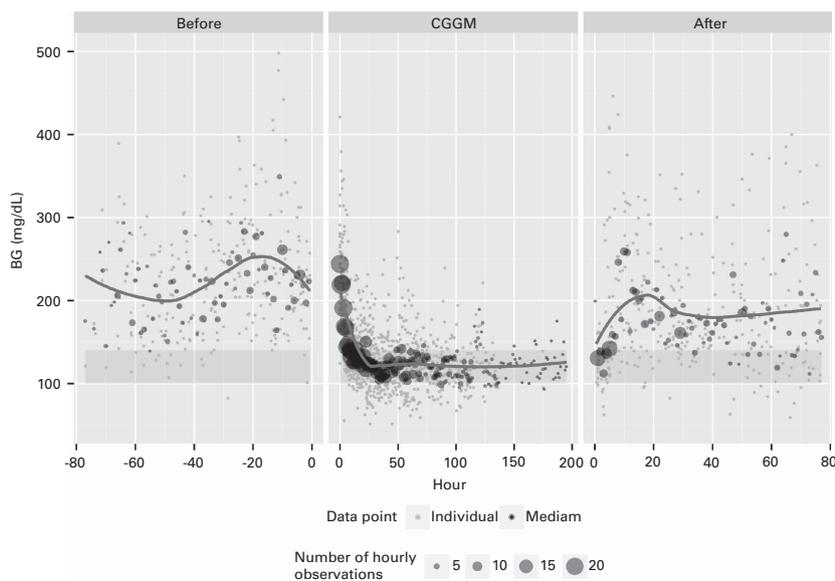


Figure 2. Blood glucose before, during and after CGGM. Green area—BG level 100–140 mg/dL. Gray dots—individual BG measurements. Black dots—median of individual BG measurements at the hour; the size of the point indicates the number of observations at that hour. Blue line—LOESS smoother to highlight trend. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

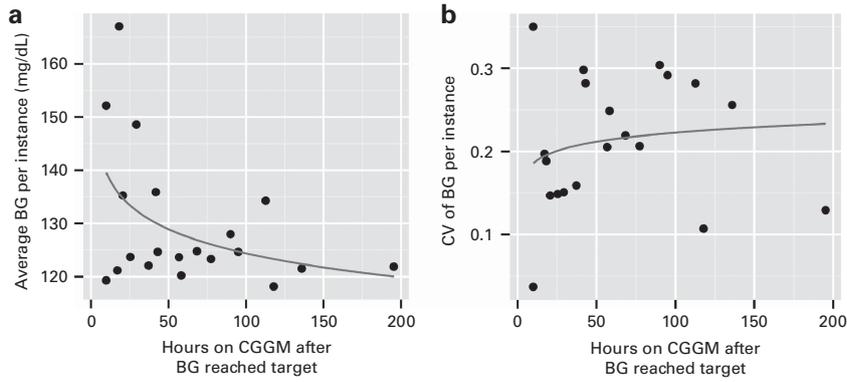


Figure 3. BG level (a) and glycemic variability (b) according to time on CGGM after reaching target range. (a) Average BG per patient according to length of stay on CGGM after reaching study BG target. Each dot represents the average BG for a patient according to his/her length of stay on CGGM after reaching study BG target. The blue line represents linear regression. (b) Coefficient of variation (CV) of BG per patient according to length of stay on CGGM after reaching BG target. Each dot represents the CV for a patient according to length of stay on CGGM after reaching BG target. The blue line represents linear regression. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

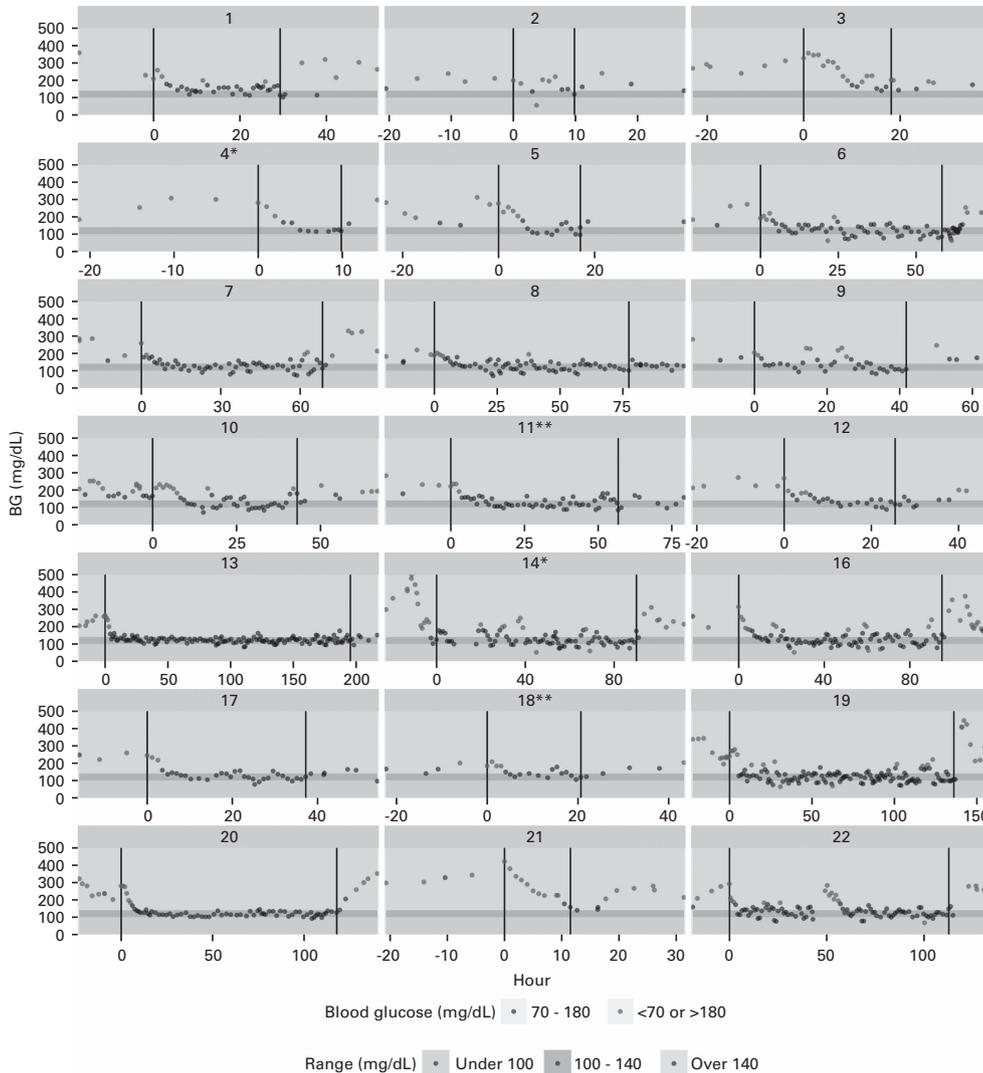


Figure 4. Blood glucose levels of all patients while on CGGM. Each graph represent one study instance. *Instances 4 and 14 are the same study participants on two separate instances. **Instances 11 and 18 are the same study participant on two separate instances. X axis—hours before/during/after CGGM. Pink area—BG < 100 mg/dL, green area—BG 100–140 mg/dL, blue area—BG > 140 mg/dL. The vertical black lines indicate the start and stop of CGGM. Red dots indicate BG levels below 70 mg/dL or above 180 mg/dL. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

Table 2. Insulin doses before, during and after CGGM

Study participant no.	GvHD status at enrollment	Daily prednisone dose (mg)	Infection status	Total Insulin dose during the last 24 h before CGGM	Range insulin dose during CGGM	Total Insulin dose during the first 24 h after CGGM
1	Active GvHD	100	CMV reactivation	0	4.1–28 u/h	Glargine 20u, Lispro 8u
2	Active GvHD	50	CMV reactivation <i>E. coli</i> bacteremia	Lispro 6u	1.6–5.9 u/h	Lispro 5u
3	Active GvHD	90	CMV reactivation	Lispro 91u	5.1–59.6 u/h	Lispro 75u, Glargine 25u hs
4	Active GvHD	176	None	Lispro 51u	1.4–5.1 u/h	Glargine 30u, Lispro 17u
5	Active GvHD	90	None	Lispro 10u	1–5.6 u/h	None
6	Active GvHD	60	None	Lispro 22u	2.4–23.8 u/h	NPH 32u, Lispro 24
7	Active GvHD	85	CMV reactivation <i>E. coli</i> bacteremia	Lispro 24u	1–10.4 u/h	Glargine 50u, Lispro 24u
8	No GvHD	0	Neutropenic fever	Lispro 5u	1.5–18.5 u/h	Lispro 5u
9	Active GvHD	200	Staph coagulase-negative bacteremia	Glargine 15u, Lispro 5u	1.4–12.3 u/h	Glargine 24u, Lispro 49u
10	Active GvHD	140	Rhinovirus	Lispro 71u	1.5–16.6 u/h	Glargine 56u, NPH 12u, Lispro 91u
11	No GvHD	0	Neutropenic fever	Lispro 13u	3–19.2 u/h	Glargine 50u, Lispro 24u
12	Active GvHD	150	CMV reactivation	Lispro 18u	1.8–8.8 u/h	Glargine 40u, Lispro 2u
13	Active GvHD	65	None	Lispro 14u	1.8–9.5 u/h	Regular 60u
14	Active GvHD	10	Sepsis picture, no source of infection was identified	Regular 70.4u	0.3–22.8u/h	Glargine 20u, Lispro 44u
16	Active GvHD	170	None	Lispro 20u	0–25.2 u/h	Glargine 48u, Lispro 38u
17	Active GvHD	150	None	Lispro 21u	0.4–6.6 u/h	NPH 30u, Lispro 22u
18	Active GvHD	160	None	Lispro 10u	0–6.8 u/h	Lispro 14u
19	Active GvHD	160	None	Lispro 16u	0.6–20.6 u/h	NPH 26u, Lispro 35u
20	Active GvHD	75	CMV enteritis	Glargine 20u, Lispro 14u	2–7.2 u/h	NPH 30u, Lispro 20u
21	No GvHD (steroids for DAH)	152	Aspergillus pneumonia	Glargine 20u, Lispro 21u	7.7–23.1 u/h	NPH 60u, Lispro 30u
22	Active GvHD	180	CMV reactivation Aspergillus pneumonia	Glargine 15u, Lispro 16u	0–11.6 u/h	Glargine 83u, regular 10u Lispro 38u,

Abbreviations: CGGM = Computer-Guided Glucose Management System; DAH = diffuse alveolar hemorrhage.

Patients on 13 of the 21 study instances remained on CGGM for > 24 h after reaching the target range. Median BG per patient was 127 mg/dL (range, 119–167 mg/dL) in the first 24 h after reaching the target, and was 121 mg/dL (range, 112–138 mg/dL) thereafter (Figure 1d). Our data suggest a trend for better BG control the longer the patient remained on CGGM (Figure 3a), but with no difference in BG variability (Figure 3b).

Figure 4 demonstrates BG levels of all patients while on CGGM.

Insulin doses required to maintain tight glucose control while on CGGM were variable (between 0 and 59.6 u/h), but were higher than the insulin doses used in the 24 h before or after CGGM. Table 2 summarizes the range of insulin doses for all patients while on CGGM and in the 24 h before and after CGGM.

DISCUSSION

Several studies have evaluated the effect of BG levels on hospitalized patients with emerging evidence that not only hyperglycemia, but also hypoglycemia and variable glucose level may have a negative effect on outcome.^{1,2,5,8,14–16,18–20,31–36} Our team and others have previously demonstrated the association between malglycemia (hyperglycemia, hypoglycemia and increased glycemic variability) and increased NRM and infections in HCT patients.^{24–26} In addition, adverse clinical consequences of hyperglycemia from total parenteral nutrition exposure during HCT were reported.³⁷ These findings raised the hypothesis that stringent glycemic control with prevention of hypoglycemia and glucose variability may improve transplant outcome. However, as demonstrated by the NICE SUGAR study, intensive glucose control may increase the risk of severe hypoglycemia.³⁵ Thus, a novel strategy is required to obtain glucose level within a stringent

range while minimizing hypoglycemia. Using *Glucommander* it was recently shown that for patients without diabetes, complications during coronary artery grafting were less, maintaining glucose level between 100 and 140 mg/dL versus level of 141–180 mg/dL.¹² As the first step to prospectively evaluate the effect of this desired degree of glucose control in the HCT setting, we evaluated the feasibility of obtaining near normoglycemia in HCT patients using a CGGM. Despite the small number of patients enrolled on the study, we demonstrated that a narrow range of glucose levels between 100 and 140 mg/dL was attained 61% of the time while on CGGM, with only 10 episodes (0.9% of BG measurements and 0.2% of total time on study) of BG lower than 70 mg/dL and with no episodes of BG lower than 40 mg/dL. This rate is significantly lower compared with other protocols. For example, in the NICE SUGAR study 6.9% of patients in the intensive therapy group had severe hypoglycemia defined as a glucose level below 40 mg/dL.³⁸ Our data, in a more difficult population, are comparable to other CGGM data, in which, among over 5000 insulin runs (over 120 000 h) 0.6% of values were found to be < 50 mg/dL.²⁸ Hypoglycemia will always remain a limiting factor of insulin therapy, but the frequency of hypoglycemia in our study is minimal as we documented no levels below 50 mg/dL and only 0.9% below 70 mg/dL.

GvHD produces a massive inflammatory response,³⁹ which may lead to insulin resistance.⁴⁰ Treatment with glucocorticoids, while effective in reducing inflammatory activation, will result in more insulin resistance and for many, hyperglycemia, as demonstrated by Pidala *et al.*⁴¹ There are further theoretical concerns that the combination of hyperglycemia and hyperinsulinemia (either endogenous or exogenous) may be maladaptive as this scenario has been shown to result in additional inflammation.⁴² On the

other hand, when enough insulin is provided to control glycemia, inflammation is actually suppressed.⁴³ As recently reviewed by Fuji *et al.* hyperglycemia causes not only impaired immune function and elevation of proinflammatory cytokines, but also causes problems with other tissues, such as endothelial dysfunction, catabolism of muscle and fat and procoagulation, all of which may be relevant in patients after allogeneic HSCT.⁴⁴ Given our original observations of increased NRM and mortality associated with malglycemia,²⁴ we hypothesized that providing enough IV insulin to meticulously control glucose levels during GvHD could add to the anti-inflammatory stimulus of the glucocorticoids and impact HCT outcomes. The primary objective of our study was to evaluate if the degree of glycemic control required in this situation was possible, and the results suggest it is indeed possible, although inflammatory cytokines were not measured.

A limitation of our study was the need for frequent (approximately once every hour) BG measurements to be entered to the CGGM software to calculate the recommended insulin dose. The frequent BG measurements by finger stick caused inconvenience to patients and nursing staff, but were essential to adjust the insulin dosing in order to maintain glucose levels within the target range. Furthermore, current standard IV insulin protocols also require hourly BG testing.^{45,46} While continuous glucose monitoring, either SC or intravascular are not current options in the inpatient setting, if these tools ever become available the ability to control glycemia should become less burdensome.^{47–51} Additional limitations of our study are the small cohort and the lack of a control arm. However this is a feasibility study, which we hope will set the stage for a larger randomized trial.

In conclusion, our study demonstrates that despite high doses of steroids, total parenteral nutrition, and unpredictable oral intake, stringent BG control without frequent hypoglycemia or high glycemic variability was achieved by using CGGM. Future studies are needed to assess the practicality of using CGGM in a multi-center setting in addition to measurement of various inflammatory markers. The ultimate goal of these studies will be to perform a larger randomized controlled trial to evaluate the impact of improved glycemic control on transplant outcome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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