Continuous Glucose Monitoring in Insulin-Treated Patients in Non-ICU Settings

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Abstract

Inpatient hyperglycemia, in patients with and without a history of diabetes, is associated with increased risk of complications, mortality, and longer hospital stay in medicine and surgical patients. Bedside capillary point of care testing is widely recommended as the preferred method for glucose monitoring and for guiding glycemic management of individual patients; however, the accuracy of most handheld glucose meters is far from optimal. Recent studies in the hospital setting have reported that the use of continuous glucose monitoring (CGM) can provide real-time information about glucose concentration, direction, and rate of change over a period of several days. Because it provides glucose values every 5-10 minutes 24 hours a day, CGM may have an advantage over point of care testing with respect to reducing the incidence of severe hypoglycemia in acute care. Real-time CGM technology may facilitate glycemic control and to reduce hypoglycemia in insulin-treated patients. Recent guidelines, however, have recommended deferring the use of CGM in the adult hospital setting until further data on accuracy and safety become available. In this study, we review the advantages and disadvantages of the use of real-time CGM in the management of dysglycemia in the hospital setting.

Keywords

continuous glucose monitoring, inpatient hyperglycemia, point of care testing, glucose monitoring

Inpatient dysglycemia—hyperglycemia, hypoglycemia, and increased glycemic variability—is common and is associated with increased risk of hospital complications and mortality. Several observational studies and intervention trials have reported a prevalence of hyperglycemia (> 140 mg/dl) in ~ 80% of critically ill and cardiac surgery patients[1,2] and in 38%-46% of non–critically ill hospitalized patients.[3,4] The development of hyperglycemia, in patients with and without a history of diabetes, is associated with increased risk of complications, mortality, and longer hospital stay.[3,5] Like hyperglycemia, inpatient hypoglycemia has been associated with higher rates of hospital complications, longer hospital stay, higher health care resource utilization, and hospital mortality, creating a J-shaped relationship between glucose levels and mortality rates.[6-9] A glucose level < 2.8 mmol/L (50 mg/dL) was reported to be associated with a mortality rate of 22.2%, compared to 2.3% in patients without hypoglycemia.[10] Increasing evidence from in vitro and human studies has indicated that oscillating glucose levels may be more dangerous than stable hyperglycemia, particularly in activating the pathways involved in the pathogenesis of diabetes complications. Glucose fluctuations result in increased oxidative stress[11] and vascular inflammation,[12] which can lead to increased cardiovascular events. Mendez et al[13] recently reported that increased glycemic variability during hospitalization is independently associated with longer hospital stay and increased mortality in non–critically ill patients.

Bedside capillary point of care (POC) testing is recommended as the preferred method for glucose monitoring and for guiding glycemic management of individual patients.[14] POC testing is usually performed before meals and at bedtime for patients who are eating[15,16] or every 4-6 hours for patients who are not eating or receiving continuous enteral nutrition. Among critically ill patients in the ICU, more frequent glucose monitoring is indicated in patients treated with continuous intravenous insulin infusion[17,18] and in patients with frequent episodes of hypoglycemia.[15,19] Unfortunately, the accuracy of most handheld glucose meters is far from optimal.[20] The Food and Drug Administration (FDA) allows for a variance of 20% for meter measurements and 10% for central laboratory results as compared to the true blood glucose level.[16,21] This accepted variance can lead to the omission of important clinical information or to the use of inappropriate therapies.

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Furthermore, patient factors such as pH changes, oxygenation status, tissue perfusion, varying hemoglobin concentrations, and other interfering hematologic factors in acutely ill patients can affect meter measurements.[21-23]

The use of continuous glucose monitoring (CGM) has evolved from being a research tool to serving as a device useful for outpatient clinical care in patients with type 1 and type 2 diabetes. Designed to successfully improve glucose control without the addition of medication in ambulatory patients, CGM provides information about glucose concentration, direction, and rate of change over a period of several days. Because it provides glucose values every 5-10 minutes 24 hours a day, CGM may have an advantage over POC testing with respect to reducing the incidence of severe hypoglycemia in acute care.[24,25] Two types of CGM device are commercially available: retrospective and real-time CGM. Retrospective CGM is a Holter-type device that measures interstitial glucose levels and stores the information over a period up to 7 days to facilitate insulin adjustment, recognition of daily blood glucose (BG) fluctuations, and prevention of hypoglycemia.[26] Its retrospective nature, however, represents a significant limitation, because patients are unable to react to BG changes before they reach abnormal ranges.[27-32] In contrast, real-time CGM technology provides current BG estimates and direction and magnitude of glucose trends, thus allowing patients to take necessary actions to reduce glycemic excursions outside a target range.[26] Real-time CGM technology has been shown to facilitate glycemic control and to reduce hypoglycemia in insulin-treated patients.[26,33-35] Recent guidelines, however, have recommended deferring the use of CGM in the adult hospital setting until further data on accuracy and safety become available. In this study, we review the advantages and disadvantages of the use of real-time CGM in the management of dysglycemia in the hospital setting.

History of BG Monitoring

Significant progress has been made since James Herrick reported in 1901 that the examination of urine for glucose was the crucial test for the diagnosis of diabetes mellitus in ambulatory patients as well as in patients with infections, cardiovascular disorders, and diabetic coma.[36] During the following decades, several investigators pioneered laboratory methods for quantitative BG estimations in the laboratory for the diagnosis and critical care management of diabetes.[37] In 1965, an Ames research team headed by Clemens developed Dextrostix, the first BG test strip, which was a paper reagent strip that used the glucose oxidase/peroxidase reaction.[20] Shortly thereafter, Boehringer Mannheim developed the Chemstrip glucose strip. A large drop of blood (50-100 μL) was applied to the reagent pad, and the pad color was visually assessed against a color chart to determine a semiquantitative BG value. Although these test strips were designed for use in doctors' offices, they were widely used in clinics, surgery departments, and

hospital wards to monitor glycemic control. Dextrostix, the first quantitative glucose device to use reflectance meters, became commercially available in 1970.[37] Despite its high cost, large size, and weight (1.2 kg) and the need to use the wash-and-blot technique to remove red blood cells, it became used in emergency departments, because it provided rapid results and a few studies reported good correlation with laboratory reference methods. Several reflectance meters requiring a smaller blood volume (20-30 ul), which were more accurate and could be removed simply by wiping with a cotton ball, were developed in subsequent years. Dextrometer, the first battery-operated meter with a digital display was launched in 1980. Since then, a large number of smaller, lightweight, portable, nonwipe technique, battery-operated, digital reflectance meters have become available for glucose monitoring. Glucose meters for self-monitoring of blood glucose (SMBG) have been effective in improving diabetes control and represent an essential tool for the management of ambulatory and hospitalized patients with diabetes and hyperglycemia.

The concept of the biosensor for measuring glucose levels was first proposed in 1962 by Clark and Lyons of the Children's Hospital of Cincinnati.[38] The first CGM prototypes, which became available for research purposes in the early 1970s, extrapolated blood through a double-lumen catheter used for the development of glucose sensor-controlled insulin infusion systems.[39,40]

In 1977, Miles Laboratories produced the Biostator, a relatively large bedside unit. The Biostator incorporates an in-line venous cannula to measure glucose and calculates the correct insulin and dextrose infusion rate on the basis of this measurement. However, the device has serious limitations in clinical practice: it needs constant supervision, is bulky, and requires the continuous withdrawing and discarding of venous blood to measure glucose levels ex vivo using an oxidase-containing membrane.[41] In the past 2 decades, considerable technological progress resulted in the regulatory approval of different continuous and semicontinuous monitors.

The first CGM device made available in the United States was the GlucoWatch biographer (no longer in use), approved in 1999 by the FDA. This device was worn like a wristwatch and provided glucose measurements every 10 minutes via transdermal extraction of interstitial fluid by reverse iontophoresis, a process by which a device extracts glucose samples from fluids in the body by applying extremely low electric currents to intact skin.[42,43] Several limitations, including skipped readings, skin irritation, and inaccuracy, kept the device from receiving clinical acceptance. Other semi-invasive continuous glucose monitors, consisting of a micropump (with a flow rate of 15-100 mL/min) and a biosensor coupled with a microdialysis system, followed. Most CGM devices continue to employ subcutaneous sensors to determine the glucose concentration in interstitial fluid. Therefore, they require frequent calibration by fingerstick tests and cannot be used for more than a few days. Some of

Table 1. Advantages, Disadvantages, and Cost of Available Continuous Glucose Monitoring (CGM) Systems.

Device	Advantages	Disadvantages	Cost
Dexcom SEVEN Plus (Dexcom)	Lightweight; can be used up to 7 days; water-resistant; transmits glucose data every 5 minutes to a handheld receiver within 6-foot range; stores glucose data up to 30 days	Invasive; requires calibration with blood glucose testing; requires a change of the sensor after 7 days	$1158 for CGMS and $349 for 4 sensors
Dexcom G4TM PLATINUM (Dexcom)	Lightweight; transmits glucose data every 5 minutes to a handheld receiver within 20-foot range; receiver with alarm alerts for high and low glucose levels and for rapidly rising or falling glucose levels	Invasive; requires calibration with blood glucose testing every 12 hours; requires a change of the sensor after 7 days	$1198 for GMS and $349 for a 4-pack of sensors
Guardian REAL-time (Medtronic)	Wireless transmitter attached to a glucose sensor; transmits average glucose to the monitor every 5 minutes; glucose sensor can be used up to 6 days; anticipates and displays glucose trends; alarm alerts for high and low glucose levels and for rapidly rising or falling glucose levels	Invasive; requires calibration with blood glucose testing; requires a change of the sensor after 3 days	$1400 for CGMS and $50 for a sensor
FreeStyle Navigator (Abbott)	Lightweight; water-resistant; measures glucose every 1 minute and transmits glucose data to the receiver within 3-meter range; glucose sensor lasts up to 5 days; receiver is a stand-alone unit with integrated blood glucose testing; early-warning alarms alert for high and low glucose levels	Invasive; requires calibration with a built-in blood glucose meter; requires a change of the sensor after 5 days	$1000 for the receiver and transmitter and $375 for a 6-pack of sensors
FreeStyle Navigator II (Abbott)	Lightweight; sensor can be used for up to 5 days; measures glucose every 1 minute; provides glucose trend and warning alarm alerts; transmits glucose data to the receiver within 30-meter range; built-in FreeStyle blood glucose meter	Invasive; requires calibration with built-in blood glucose meter; requires a change of the sensor after 5 days	$1524 for the receiver and transmitter and $64.20 for a sensor; daily cost of $7.50

the recently developed CGM devices are wireless; their sensors are inserted into the subcutaneous tissue of the abdomen or upper arm. Important features of available CGM devices are listed in Table 1.

Glucose Monitoring in the Non–Critical Care Setting

Recent guidelines recommend the use of POC testing as the preferred method for guiding the inpatient glycemic management of individual patients.[44] Matching the timing of POC testing with nutritional intake and the diabetes medication regimen in the hospital setting is consistent with recommendations for the outpatient setting. POC testing is usually performed 4 times a day: before meals and at bedtime for patients who are eating[15,16] and every 4-6 hours for patients who are NPO or receiving continuous enteral nutrition. More frequent glucose monitoring is indicated in patients treated with continuous intravenous insulin infusion,[17,18] in patients with frequent episodes of hypoglycemia,[15,19] and after a medication change that could alter glycemic control, such as corticosteroid use or abrupt discontinuation of enteral or parenteral nutrition.[45-47]

Even though quality control programs are essential to meeting FDA requirements and to maintaining the accuracy

and reliability of BG testing,[16] a 20% variance between BG measurements derived from POC testing and the laboratory value is considered acceptable.[16,21] Recent reports have advocated improvement or tightening of POC meter accuracy standards.[21] However, capillary BG values continue to vary between POC meters, especially at high or low hemoglobin levels, at low tissue perfusion, and in the presence of some extraneous substances.[20,48] Furthermore, POC testing involves potential inaccuracies due to issues inherent to the technology, variability between different batches of test strips, varying hemoglobin concentrations, and other interfering hematologic factors in acutely ill patients.[21-23] A study of 5 commonly used glucose meters conducted by the Centers for Disease Control determined that mean differences from a central laboratory method were as high as 32% and found a coefficient of variation of 6%-11% in tests performed by individual trained medical technologists.[21]

Use of CGM Devices in the Hospital Setting

Comparison studies on the efficacy and clinical benefits of CGM devices and SMBG have produced mixed results, in part due to small sample sizes and variability across studies, including differences in age of subjects, in type of CGM

Table 2. Clinical Trials Comparing Glucose Monitoring by Point of Care (POC) testing and Continuous Glucose Monitoring (CGM).

Author	Population	Intervention	Outcome
Corstjens et al 2006[53]	19 medical ICU patients	165 paired samples; CGM sensor validated against arterial blood gas/glucose analyzer	100% of sensor values within zones A and B of Clarke error grid; very good correlation ($r = .89$)
De Block et al 2006[54]	50 adults (DM = 20, no-DM = 30) treated with IV or SC insulin in medical ICU	48-hour CGM with SC glucose sensor (GlucoDay) vs arterial glucose testing	No difference in glucose control
Piper et al 2006[55]	20 children during cardiac bypass surgery	165 paired samples; CGM sensor was inserted; arterial blood glucose measured by laboratory for comparisons	98.8% of sensor values within zones A and B; no interference of sensor performance with inotrope use or body edema
Yamashita et al 2009[56]	50 patients scheduled for routine surgery were studied in surgical intensive care unit (ICU) of a university hospital	200 paired samples; CGM sensor validated against arterial blood gas/glucose analyzer	100% of sensor values within zones A and B; very good correlation, $r = .96$
Rabiee et al 2009[57]	19 patients on insulin infusion were enrolled in this 7-day study (13 = surgical intensive care unit, 6 = burn intensive care unit)	1065 paired samples; CMG sensor validated against capillary POC values and glucose analyzer	99.25% of sensor values within zones A and B
Holzinger et al 2009[24]	50 ICU patients with circulatory shock requiring norepinephrine and IV insulin therapy	736 paired samples; CMG sensor validated against laboratory glucose values	Mean difference between groups was 0.08 mmol/l; no interference of sensor performance with circulatory shock or norepinephrine use
Ryan et al 2009[58]	Case report of a patient with type 1 diabetes undergoing orthopedic surgery treated with basal prandial regimen	POC capillary glucose measurement plus blinded CGM	Hypoglycemic threshold detected with CGM 4.5 hours before severe hypoglycemia
Holzinger et al 2010[25]	Randomized clinical trial in 124 mechanically ventilated ICU patients on IV insulin infusion	63 CGM and 61 POC glucose testing	No difference on mean daily glucose control; lower rate of hypoglycemia with CGM
Rodriguez-Quintanilla et al 2013[59]	Pilot, nonrandomized, unblinded clinical trial; 16 patients with acute coronary syndrome treated with IV insulin infusion	Conventional group with POC testing and insulin adjustment every 4 hours vs intervention CGM and insulin adjustment every 1 hour	Conventional group resulted in shorter time to achieve normoglycemia
Kopecky et al 2013[60]	24 postcardiac surgery patients treated with IV insulin infusion	CGM compared to glucose control in enhanced model predictive control (eMPC) algorithm	No differences in glucose control between groups
Burt et al 2013[61]	Observational study of 26 DM patients with type 1 and type 2 diabetes in general wards treated with basal prandial insulin treatment	72-hour CGM and capillary POC testing before meals and at bedtime	No difference in the mean daily glucose levels; higher number of hyperglycemia and hypoglycemia events detected by CGM
Gomez et al 2013[52]	Randomized study of 40 insulin-naïve patients with type 2 in general wards treated with basal prandial insulin for ≥ 3 days	CGM compared to POC testing; blinded CGM data; POC testing before and 2 hours after meals, at bedtime, and at 3:00 AM	No difference in daily glucose; similar number of patients with hypoglycemia, but CGM detected more events

utilized (retrospective versus real time), and in duration of follow-up.[49,50] In a recent meta-analysis of ambulatory patients with diabetes, we reported that CGM is associated with significantly better incremental benefit in HbA1c reduction compared to SMBG.[51] Greater benefits of CGM relative to SMBG were observed in studies of more than 12 weeks of intervention and in subjects > 25 years of age. In addition, CGM resulted in less time spent in hypoglycemic ranges

than did SMBG, but there was no difference in the frequency of hypoglycemia.[51]

Recent studies have suggested that continuous BG monitoring devices may be helpful in reducing the incidence of severe hypoglycemia in acute care[24,25] (Table 1). In some small clinical trials, CGM devices have been shown to improve hypoglycemia and hyperglycemia detection when compared with POC capillary glucose measurements (Table 2).

The majority of ICU studies have reported good correlation between glucose values measured by interstitial CGM and arterial/capillary and laboratory measurements, with most CGM measurements falling within zones A and B of the Clarke error grid. Recent studies in non-ICU wards comparing CGM interstitial glucose testing with capillary POC testing reported no differences in mean daily glucose, but CGM testing detected a higher rate of postprandial hyperglycemic excursions and of hypoglycemic events (Table 2).

In a recent prospective study, we compared inpatient glycemic control by CGM (Sofsensor iPro 2, Medtronic) and capillary POC testing in general medicine patients with type 2 diabetes treated with a basal bolus insulin regimen for ≥ 3 days.[52] Both patients and hospital staff were blinded to the CGM data. POC testing measurements were performed before meals, 2 hours after meals, at bedtime, and at 3:00 AM. The primary outcomes were differences in daily BG and in the number of hypoglycemia (< 70 mg/dl) and hyperglycemia (> 180 mg/dl) events between groups. A total of 40 insulin-naïve patients (age: 65.8 ± 8 years, DM duration: 14.7 ± 9 years, admission BG: 251 ± 9 mg/dl, A1C: $9.7 \pm 2.4\%$, ± SD) were treated with glargine and glulisine at a starting total dose of 0.4 U/kg/day if BG was between 140-200 mg/dl and at a dose of 0.5 U/kg/day if BG was between 200-400 mg/dl, given half as glargine once daily and half as glulisine before meals. We observed no difference in daily BG after the first day of treatment by CGM and POC testing (Table 3). There were 10 patients with BG < 70 mg/dl recognized by both methods, but CGM detected a higher number of events (55 versus 12, $P < .0001$) than POC testing (Table 3), with 40% occurring between breakfast and dinner and 60% between dinner and 6:00 AM. A total of 26.3% of hypoglycemia events were asymptomatic, and most of these events (86.7%) were identified only by CGM. The proportion of BG >180 mg/dl identified by CGM was 36.8%, whereas the proportion identified by POC testing was 42.1%.[52] Our observations were in agreement with previous reports and indicated that the use of CGM did not improve glucose control, but recognized a greater number of hypoglycemic events compared to POC testing. Our study indicated the potential benefit of using real-time CGM in the hospital to detect hypoglycemia in a more timely fashion compared to POC testing. However, more studies with a larger number of patients are needed to determine the accuracy and reliability of continuous BG monitoring devices in hospitalized patients.

In summary, although CGM technology is promising, few studies have tested its use in the acute care setting. Therefore, the Endocrine Society advises against its use because extensive evidence regarding CGM's safety and efficacy is lacking.[5] This expert committee considered that maintaining direct access to the blood on a continuous basis for an extended period of time is impractical due to lack of reliability in terms of accuracy and the precision of the various systems, and due to the high cost of the use of CGM devices in the general inpatient (non-ICU) setting. In addition, recent

Table 3. Number of Hypoglycemic Events Detected by Point of Care (POC) Testing and Continuous Glucose Monitoring (CGM) Device During Treatment With Basal Bolus Insulin in Patients With Type 2 Diabetes.[52]

	POC	CMG	*P* value
Number of hypoglycemic events	12	55	.0001
Number of asymptomatic hypoglycemic events	1	13	.0004
Nocturnal hypoglycemia	0	4	.0399
Daytime hypoglycemia	1	9	.0066

guidelines on inpatient glycemic control recommended against intensive inpatient glucose control for the majority of non-ICU patients.[14,44] Departing from historic intensive insulin regimes with recent guidelines no longer recommending tight glucose targets may also reduce the need to use CGM devices in non–critically ill patients.

Abbreviations

BG, blood glucose; CGM, continuous glucose monitoring; DM, diabetes mellitus; FDA, Food and Drug Administration; ICU, intensive care unit; POC, point of care; SMBG, self-monitoring blood glucose.

Declaration of Conflicting Interests

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References

1. Schmeltz LR, DeSantis AJ, Thiyagarajan V, et al. Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. *Diabetes Care.* 2007;30(4):823-828.
2. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001;345(19):1359-1367.

3. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87(3):978-982.

4. Cook CB, Kongable GL, Potter DJ, Abad VJ, Leija DE, Anderson M. Inpatient glucose control: a glycemic survey of 126 U.S. hospitals. *J Hosp Med*. 2009;4(9):E7-E14.

5. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg*. 2013;257(1):8-14.

6. Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc*. 2010;85(3): 217-224.

7. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med*. 2007;35(10):2262-2267.

8. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367(12): 1108-1118.

9. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation*. 2008;117(8):1018-1027.

10. Stagnaro-Green A, Barton MK, Linekin PL, Corkery E, deBeer K, Roman SH. Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia. *Mt Sinai J Med*. 1995;62(6):422-426.

11. Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature*. 2000;404(6779):787-790.

12. Siegelaar SE, Holleman F, Hoekstra JB, DeVries JH. Glucose variability; does it matter? *Endocr Rev*. 2010;31(2):171-182.

13. Mendez CE, Mok KT, Ata A, Tanenberg RJ, Calles-Escandon J, Umpierrez GE. Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care*. 2013;36(12):4091-4097.

14. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care*. 2009;32(6):1119-1131.

15. Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27(2):553-597.

16. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract*. 2009;15(4):353-369.

17. Juneja R, Foster SA, Whiteman D, Fahrbach JL. The nuts and bolts of subcutaneous insulin therapy in non-critical care hospital settings. *Postgrad Med*. 2010;122(1):153-162.

18. Smiley D, Rhee M, Peng L, et al. Safety and efficacy of continuous insulin infusion in noncritical care settings. *J Hosp Med*. 2010;5(4):212-217.

19. Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med*. 2006;355(18):1903-1911.

20. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. *Diabetes Care*. 2007;30(2):403-409.

21. Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? *Clin Chem*. 2009;55(1):18-20.

22. Vlasselaers D, Herpe TV, Milants I, et al. Blood glucose measurements in arterial blood of intensive care unit patients submitted to tight glycemic control: agreement between bedside tests. *J Diabetes Sci Technol*. 2008;2(6):932-938.

23. Cembrowski GS, Tran DV, Slater-Maclean L, Chin D, Gibney RT, Jacka M. Could susceptibility to low hematocrit interference have compromised the results of the NICE-SUGAR trial? *Clin Chem*. 2010;56(7):1193-1195.

24. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PG, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. *Intensive Care Med*. 2009;35(8):1383-1389.

25. Holzinger U, Warszawska J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. *Diabetes Care*. 2010;33(3):467-472.

26. Skyler JS. Continuous glucose monitoring: an overview of its development. *Diabetes Technol Ther*. 2009;11(S1):S5-S10.

27. Weintrob N, Schechter A, Benzaquen H, et al. Glycemic patterns detected by continuous subcutaneous glucose sensing in children and adolescents with type 1 diabetes mellitus treated by multiple daily injections vs continuous subcutaneous insulin infusion. *Arch Pediatr Adolesc Med*. 2004;158(7):677-684.

28. Buckingham B, Block J, Wilson DM. Continuous glucose monitoring. *Curr Opin Endocrinol Diabetes*. 2005;12: 273-279.

29. Cryer P. Diverse causes of hypoglycemia associated autonomic failure in diabetes. *N Engl J Med*. 2004;350:2272-2279.

30. Diess D, Bolinder J, Riveline J, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*. 2006;29(12):2730-2732.

31. Klonoff D. Continuous glucose monitoring delivers detailed diabetes data. *Point of Care*. 2006;5:105-115.

32. Rolfing CL, Weidmyer H, Little RR, England JD, Tennel A, Goldstein D. Defining the relationship between plasma glucose and HbA1c. *Diabetes Care*. 2002;25:275-278.

33. Doyle EA, Weinzimer SA, Steffen AT, Ahern JH, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care*. 2004;27:1554-1558.

34. Hirsch IB, Abelseth J, Bode BW, et al. Sensor augmented insulin pump therapy: results of the first randomized treat to target study. *Diabetes Technol Ther*. 2008;10:377-383.

35. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Research Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359:1464-1476.

36. Herrick JB. The diagnosis of diabetes mellitus. *JAMA*. 1901;36(4):223-225.

37. Clarke SF, Foster JR. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. *Br J Biomed Sci*. 2012;69(2):83-93.

38. Clark LC Jr, Lyons C. Electrode systems for continuous monitoring in cardiovascular surgery. *Ann NY Acad Sci*. 1962;102:29-45.

39. Albisser AM, Leibel BS, Ewart TG, et al. Clinical control of diabetes by the artificial pancreas. *Diabetes*. 1974;23(5):397-404.

40. Pfeiffer EF, Thum C, Clemens AH. The artificial beta cell—a continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm Metab Res*. 1974;6(5):339-342.

41. Plank J, Blaha J, Cordingley J, et al. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. *Diabetes Care*. 2006;29(2):271-276.

42. Skyler JS. CGM—a technology in evolution. *Diabetes Technol Ther*. 2009;11(2):63-64.

43. Tamada JA, Bohannon NJ, Potts RO. Measurement of glucose in diabetic subjects using noninvasive transdermal extraction. *Nat Med*. 1995;1(11):1198-1201.

44. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(1):16-38.

45. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract*. 2006;12(4):358-362.

46. Seley JJ, D'Hondt N, Longo R, et al. Position statement: inpatient glycemic control. *Diabetes Educator*. 2009;35(suppl 3):65-69.

47. Association AD. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33(suppl 1):S11-S61.

48. Boyd JC, Bruns DE. Quality specifications for glucose meters: assessment by simulation modeling of errors in insulin dose. *Clin Chem*. 2001;47(2):209-214.

49. Chetty VT, Almulla A, Odueyungbo A, Thabane L. The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in type I diabetic patients: a systematic review. *Diabetes Res Clin Pract*. 2008;81(1):79-87.

50. Golicki DT, Golicka D, Groele L, Pankowska E. Continuous glucose monitoring system in children with type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia*. 2008;51(2):233-240.

51. Floyd B, Chandra P, Hall S, et al. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol*. 2012;6(5):1094-1102.

52. Gomez AM, Umpierrez GE, Aschner P, Herrera F, Muñoz O, Rubio C. Comparison of inpatient glycaemic control by continuous glucose monitoring (CGM) and capillary point-of-care (POC) testing in general medicine patients with type 2 diabetes. *Diabetologia*. 2013;56(suppl 1):S1-S566.

53. Corstjens AM, Ligtenberg JJ, van der Horst IC, et al. Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients. *Crit Care*. 2006;10(5):R135.

54. De Block C, Manuel YKB, Van Gaal L, Rogiers P. Intensive insulin therapy in the intensive care unit: assessment by continuous glucose monitoring. *Diabetes Care*. 2006;29(8):1750-1756.

55. Piper HG, Alexander JL, Shukla A, et al. Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. *Pediatrics*. 2006;118(3):1176-1184.

56. Yamashita K, Okabayashi T, Yokoyama T, et al. Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. *Acta Anaesthesiol Scand*. 2009;53(1):66-71.

57. Rabiee A, Andreasik V, Abu-Hamdah R, et al. Numerical and clinical accuracy of a continuous glucose monitoring system during intravenous insulin therapy in the surgical and burn intensive care units. *J Diabetes Sci Technol*. 2009;3(4):951-959.

58. Ryan MT, Savarese VW, Hipszer B, et al. Continuous glucose monitor shows potential for early hypoglycemia detection in hospitalized patients. *Diabetes Technol Ther*. 2009;11(11):745-747.

59. Rodriguez-Quintanilla KA, Lavalle-Gonzalez FJ, Mancillas-Adame LG, Zapata-Garrido AJ, Villarreal-Perez JZ, Tamez-Perez HE. Continuous glucose monitoring in acute coronary syndrome. *Arch Cardiol Mex*. 2013;83(4):237-243.

60. Kopecky P, Mraz M, Blaha J, et al. The use of continuous glucose monitoring combined with computer-based eMPC algorithm for tight glucose control in cardiosurgical ICU. *Biomed Res Int*. 2013;2013:186439.

61. Burt MG, Roberts GW, Aguilar-Loza NR, Stranks SN. Brief report: comparison of continuous glucose monitoring and finger-prick blood glucose levels in hospitalized patients administered basal-bolus insulin. *Diabetes Technol Ther*. 2013;15(3):241-245.