Blood Glucose Monitoring In Pediatric Patients—Looking Toward Better Diabetes Management and Perspectives for the Future

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DOI: 10.17925/USE.2010.06.1.54

Abstract

Self-blood glucose monitoring (SBGM) is an important component of day-to-day diabetes management for children and their families. Despite some recent concerns in terms of its analytical accuracy, it has been used successfully to implement intensive glucose control in the Diabetes Control and Complications Trial, reduce glycated hemoglobin (HbA_{1c}) levels, prevent acute complications, and make it possible for children to attend school and participate in sports activities safely. While still in its infancy, continuous glucose monitoring (CGM) has been shown to be useful in reducing the occurrence of nocturnal hypoglycemia, lowering HbA_{1c} levels, and reducing glycemic variability. Its analytical accuracy has prevented its approval as an alternative to SBGM for insulin decision-making. However, it has made possible the development and testing of closed-loop 'artificial pancreas' systems for controlling glucose levels in adults and adolescents.

Keywords

Self-blood glucose monitoring, continuous glucose monitoring, clinical accuracy, glycemic variability, hypoglycemia, hyperglycemia, artificial pancreas

Disclosure: The author has no conflicts of interest to declare.
Acknowledgment: Supported in part by a National Institutes of Health (NIH) grant RO1 DK 51562.
Received: August 10, 2010 **Accepted:** October 26, 2010 **Citation:** *US Endocrinology*, 2010;6:54–7
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Introduced into patient-directed self–management in the early 1980s, self-blood glucose monitoring (SBGM) is now recognized as integral to standard of care diabetes treatment for all age groups.[1] Indeed, along with the development of stable and reproducible glycated hemoglobin (HbA_{1c}) assays, SBGM made possible the achievement of intensive therapy and the design and conduct of the Diabetes Control and Complications Trial (DCCT).[2] Today, most individuals with type 1 diabetes use SBGM test results multiple times daily to adjust their treatment decisions. SBGM in pediatric patients is neither unique nor particularly different from that in adults. However, the improvements in SBGM technology, such as smaller sample size, alternate site testing, and improvements in accuracy, have been particularly welcomed by children and their parents.[3] The next generation of glucose monitoring, continuous glucose monitoring (CGM), has been studied extensively in children and its extension to the development of closed-loop (artificial pancreas) insulin-delivery systems is a long-awaited dream.

Self-blood Glucose Monitoring

Accuracy of Self-blood Glucose Monitoring Devices

Even though SBGM devices have become smaller, more user friendly, and less susceptible to error from interfering substances, considerable concerns remain about their ability to produce reliable and reproducible results.[4,5] Accuracy of SBGM devices is described in both analytical and clinical terms. Analytical accuracy refers to standard statistical analyses that compare meter-generated glucose readings to simultaneous reference system results. Terms such as absolute and relative absolute differences are often used to describe these relationships as are correlation coefficients and linear regression equations. The US Food and Drug Administration (FDA) requires new devices to achieve 95% analytical accuracy as measured by International Standards Organization (ISO 15197) criteria.[4] These criteria state that meter readings should be within 20% of reference values when the reference is >75mg/dl and within 15mg/dl of the reference when that value is ≤75mg/dl.

'Clinical accuracy' refers to SBGM devices that produce readings that can result in clinically accurate treatment decisions.[6] While analytical and clinical accuracy often coincide, this is not always the case. For instance, a correlation coefficient for a large data set may be highly significant across the entire BG range, but differ significantly in the three critical BG ranges—hypoglycemia, euglycemia, and hyperglycemia.[7] Our research group developed error grid analysis (EGA) as a method for quantifying clinical accuracy of patient-determined BG values.[6] EGA categorizes the relationship between a patient-generated BG level and a reference BG level in terms of the clinical status that would result from a treatment decision based on a patient-generated result. Parkes

et al., have developed the consensus error grid (CEG), a similar method for describing clinical accuracy of SBGM.[8] Both methods emphasize the importance of obtaining clinically accurate information across the entire BG range (hypoglycemia, euglycemia, and hyperglycemia).

The EGA divides the reference versus SBGM BG graph into five zones of clinical accuracy (see *Figure 1*). The basic assumptions of EGA are that the target BG range is between 70 and 180mg/dl and that patient-generated BG values outside that range will be treated according to rules suggested by the healthcare provider. Zone A (upper and lower) data pairs represent patient-generated values within 20% of the reference values and/or <70mg/dl when the reference is <70mg/dl. Points in zone A are categorized as clinically accurate because they could lead to accurate treatment decisions. Zone C (upper and lower) data pairs represent possible 'overcorrection errors' as patient-generated values in these zones might trigger treatment responses that could result in BG values outside the target range. Zones D (upper and lower) values are failure to treat errors because the patient-generated values are within the target range when the reference value is either low (<70mg/dl) or high (>240mg/dl). Zone E values are erroneous errors where the patient-generated values are either high (>180mg/dl) when the reference is low (<70mg/dl) or low (<70mg/dl) when the reference is high (>240mg/dl). Patient self-treatment based on these errors could result in serious hypoglycemia or hyperglycemia. Zone B data pairs are those where the patient-generated value deviates from the reference by >20%, but may not result in clinically significant treatment errors. They are designated clinically acceptable.

EGA has been used by most manufacturers of SBGM devices to demonstrate the clinical accuracy of their meters and together with statistical analyses were reported to the FDA as part of pre-marketing proposals.[4] In the original presentation of the EGA, results from a variety of SBGM devices were presented.[6] In no case was the clinically accurate/acceptable (zones A + B) percentage <94%. Therefore, with more than 20 years of data it could reasonably be assumed that the clinical accuracy of SBGM systems analyzed using either EGA or CEG is sufficient to permit patients to make appropriate treatment decisions. However, it should be emphasized that this is a level of accuracy deemed acceptable for patients who are self-managing their diabetes. SBGM devices may not be sufficiently accurate for use in other situations such as titrating insulin doses in acutely ill patients in an intensive care unit (ICU) setting or for diagnosing diabetes.[9]

The FDA held a public meeting in March 2010 on 'Blood Glucose Meters' and invited members of academia, business, and patient with diabetes support groups to discuss their experiences with SBGM accuracy and make suggestions for changing accuracy standards. A synopsis of the meeting concluded that while there are two types of standards for reporting accuracy—regulatory and clinical—they are not always in agreement. The FDA was challenged to decide on an acceptable percentage of data pairs that should fall into each of the five zones of the EGA. In other words, clinical accuracy standards need to be strengthened if SBGM devices are to be used to monitor BG levels in situations more critical than routine outpatient settings. Optimal BG target ranges and accuracy required for different clinical situations such as hospital or ICU use, or tight glycemic control needs to be identified and reagent strips need to be labeled to reflect both their analytical and clinical performance.

Figure 1: Error-grid Analysis

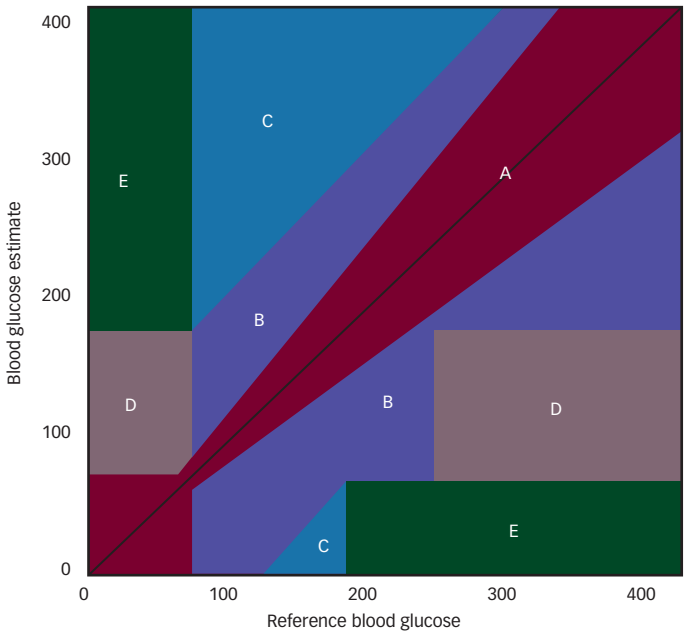

Table 1: Uses of Self-blood Glucose Monitoring

Daily management decisions
Intensive therapy
Prevention of severe hypoglycemia
Reduction of glycated hemoglobin
Management of illness/prevention of diabetic ketoacidosis

There are other important sources of error in obtaining a BG reading from a SBGM device that do not relate to the performance of the meter. Such errors might be the result of insufficient cleansing of the fingertip, inappropriate squeezing to obtain a drop of blood, failure to match calibration codes to strips, and incorrect displays (mmol instead of mg/dl) to name a few.

Uses of Self-blood Glucose Monitoring Devices

As stated earlier, SBGM was designed for patient use in day to day and hour to hour clinical decision-making. To pediatricians and parents for whom SBGM has always been a part of routine clinical diabetes management, the vast improvement in glycemic monitoring afforded by these devices is often overlooked. SBGM replaced urine glucose tests, which were difficult to obtain, especially when the patient was outside of the home, wearing diapers, or ill. At best, urine testing reflects previous glycemia rather than immediate glucose levels. Thus, the information provided by SBGM and the ease with which the results are obtained have made it possible to manage diabetes in a variety of outpatient situations (see *Table 1*). Patients, including children and their parents, have successfully used these systems to achieve a level of intensive glucose control sufficient to demonstrate the relationship between glycemia and

Table 2: Uses of Continuous Glucose Monitoring

Replacement for self-blood glucose monitoring
Prevention of hypoglycemia
Reduction of glycated hemoglobin
Reduction of glycemic variability
Clinical research studies
Development of artificial pancreas

the risk of long-term microvascular complications in the DCCT.[2] Parents have used the systems to monitor overnight BG levels to prevent serious nocturnal hypoglycemia and during illness to prevent diabetic ketoacidosis. Indeed, it has been shown that the frequency of SBGM testing is related to both lower HbA_{1c} levels and to the occurrence of acute complications such as ketoacidosis and/or hypoglycemia.[10] Along with multiple daily insulin injection therapy, SBGM has revolutionized the way in which children with diabetes are monitored and treated within school systems and in daycare centers.[11,12] Nurses, other school personnel, and care providers use the systems to assist the child with treatment decisions and keep him/her safe throughout the school day or while apart from their parents.[13] Athletes and their coaches use SBGM data to individualize treatment scenarios to prevent hypoglycemia and/or hyperglycemia and thus expand the opportunities available for physical activity.

Over the past few years, studies have reported the importance of maintaining BG levels within narrow limits (80–110mg/dl) in order to reduced morbidity in critically ill adults.[14,15] Initial studies demonstrating this reduction relied on arterial blood gas/glucose analyzers to measure BG levels. Subsequent studies using SBGM devices failed to show similar positive results[16] and it has been suggested that SBGM results are not sufficiently accurate to use in such critical situations.[9,17] Few of these studies have been performed in critically ill pediatric populations even though 'critical illness hyperglycemia' is prevalent and associated with poor outcomes.[18–20] Since hypoglycemia has been frequently reported in both children and adults being treated with 'tight glucose control' insulin-dosing algorithms, SBGM systems may not be the method of choice for measuring BG levels in these hospitalized patients.[9]

Continuous Glucose Monitoring

CGM was developed and introduced into diabetes care during the past decade. The concept of continuous monitoring is attractive to both healthcare professionals and to patients and their families because CGM 'fills in' critical pieces of information that are missing from SBGM data. In addition to providing glucose readings every one to five minutes, these systems also calculate and display the rate and direction of glucose change. Thus, patients no longer have to estimate whether their BG level is rapidly or slowly rising or falling, based on recall of previous BG readings, most recent insulin, food and exercise, and current subjective symptoms associated with their previous high or low BG levels. Such critical information is displayed on the liquid crystal display (LCD) screen of a handheld receiver. A reading of 100mg/dl no longer sits alone as an isolated value. It is now accompanied by the information needed to make an accurate treatment decision. The analogy between a digital snapshot and a video recording is often used to explain the importance of this additional information.[21] The clinical applications of CGM that have been explored to date include replacement for SBGM testing, prevention of hypoglycemia, reduction in HbA_{1c} values, reduction of glycemia variability, evaluation of the effects of new drugs or other treatments on glycemia, and the development of a closed-loop artificial pancreas for insulin delivery (see *Table 2*). Much of the data collected with CGM have been conducted by the Diabetes Research in Children Network (DirectNet) study group, a National Institutes of Health (NIH)-funded consortium of diabetes centers with strong clinical research programs.

Accuracy of Continuous Glucose Monitoring

Three CGM devices (Guardian RT, Medtronic, Northridge, CA; Freestyle Navigator, Abbott Diabetes Care, Alameda, CA; DexCom STS-7, DexCom, Inc, San Diego, CA) have been approved by the FDA for outpatient use as adjuncts to, but not replacements for, SBGM. It is recommended that treatment decisions not be based on CGM results alone, but that BG be measured with a SBGM device before any treatment decision is initiated. CGM systems do not measure BG levels rather they measure interstitial glucose levels that usually lag behind BG levels and that lag time can vary depending on the rate of BG change. Analytical accuracy as well as clinical accuracy of these new systems is not similar to SBGM accuracy, especially when the BG level is low (<70mg/dl).[22] Unfortunately, the criteria for marketing approval for these devices is identical to that for SBGM systems and does not take into account the additional clinical information presented with each glucose reading. Our research group has modified the EGA to take into account the lag time between BG and interstitial glucose based on the rate of BG change and added a rate error grid to quantify the clinical importance of accuracy of rate and direction of change CGM results.[21] It is important that clinical accuracy is calculated and reported separately for each of the critical BG ranges (hypoglycemia <70mg/dl, euglycemia 70–180mg/dl, hyperglycemia >180mg/dl). When used with currently recommended insulin dosing algorithms, recent evidence suggests that CGM results within the euglycemic or hyperglycemic ranges can be associated with clinically accurate treatment decisions.[23]

The potential for current CGM systems to serve as hypoglycemia alarms is limited to some extent by their level of analytical and clinical accuracy.[22,24,25] When alarm thresholds are set higher than the low BG target, the sensitivity of the systems increase. In other words, setting the alarm at 80mg/dl to detect BG levels of 70mg/dl detects more BG <70mg/dl than setting the alarm at 70mg/dl.[24,25] However, that increase in sensitivity is associated with a significant increase in false-positive alarms, which is a nuisance to patients and parents and could result in terminating the use of the system. Despite this shortcoming, CGM has provided important information concerning the previously unreported significant amount of time children spend with low BG overnight.[26–28] Since CGM systems calculate rate and direction of BG change, they are able to use algorithms to predict impending hypoglycemia.[29,30] Such information has been used successfully in 'partial' closed-loop systems to signal the termination of basal insulin infusion for up to 90 minutes or until glucose levels rise to euglycemia. Partial closed-loop systems used to prevent nocturnal hypoglycemic are currently being marketed in Europe.

Although early studies of CGM use demonstrated modest reductions in HbA_{1c} levels among patients unblinded to their CGM results, the most

complete information in terms of this effect comes from the Juvenile Diabetes Research Foundation (JDRF) sponsored a six-month prospective study of CGM use and its effects in children and adults.[31] Adults (age >25 years of age) significantly reduced their HbA_{1c} levels while children (8–14 years of age) and adolescents (14–25 years of age) did not. Adults used CGM six or more days a week more frequently than adolescents (83 versus 30%) and recorded more time (minutes/day) with glucose levels within the 70–180mg/dl target range. This suggests that CGM use can be associated with a reduction in glycemic variability. Other investigators have shown reductions in HbA_{1c} as well as increases in time spent within the 71–180mg/dl target range in children as young as three years of age.[32,33] These improvements in glycemic control were also related to frequency of CGM use.

The ability to record glucose continuously permits the evaluation of effects of new treatments that may not have been observable from routine SBGM and HbA_{1c} data alone. For instance, in a study of the drug Pramlintide in adults with type 1 diabetes, there was no difference in mean BG levels or in HbA_{1c} levels between the controls and the treatment group. But a statistically significant reduction in rate of BG change was observed in the treatment group, suggesting an effect of the agent on glycemic variability.[34] Others have used CGM data to evaluate the actions of different insulin regimens on glucose levels and variability.[35,36]

Perhaps the most exciting research that CGM has enabled is the development of the closed-loop artificial pancreas.[37–39] The development of CGM was a critical missing piece in closing the loop, as sophisticated insulin-infusion pumps have been used routinely for years. Current research has evolved into the testing of various control algorithms which use CGM data to guide intermittent insulin infusions.[29,30,40] This rapidly developing field holds great promise for children with type 1 diabetes and their parents.

CGM accuracy continues to improve with each new generation of sensors. However, its general use has been limited by re-imbursement matters and by a reluctance of the diabetes community to embrace its use. Currently, third party re-imbursement for CGM use has been limited to patients with recurrent BG <50mg/dl or to those with documented hypoglycemic unawareness. Other limitations and barriers to it use in children and adolescents, alluded to in the JDRF continuous monitoring study, need to be studied further.[31] Enthusiasm for continued use of this technology appears to wane over a relatively short (<12 months) period of time.

Conclusions

When used in accordance with manufacturer's recommendations and a healthcare professional's recommended treatment algorithm, SBGM has proved to be a standard of care reliable method for day-to-day treatment decisions for adults and children with type 1 diabetes. Its use been associated with reductions in average glucose levels (HbA_{1c}), glycemic variability, severe hypoglycemia, and diabetic ketoacidosis.

Analytical accuracy of SBGM systems will need to improve if they are to be used in critically ill hospitalized children and adults to adjust insulin infusions safely as part of tight glucose control protocols. SBGM should be a part of each child's school care plan. Indeed, the importance of maintaining relatively euglycemic BG levels during school is supported by recent evidence suggesting that both hypo- and hyperglycemia have negative effects on cognitive function.[41]

On the other hand, CGM is in its infancy. It clearly produces glucose readings that are less analytically and clinically accurate than those generated by SBGM devices, but the additional information that CGM data communicates can more than offset this inaccuracy. As these systems become more the accurate, their use in new and more sophisticated applications can be anticipated. The potential changes in diabetes care which this powerful new monitoring tool may be expected to produce include marked reductions in severe hypoglycemia, glycemic variability, HbA_{1c}, and by extension acute and long-term complications of type 1 diabetes. The role of CGM systems in the development of a practical closed-loop artificial pancreas for outpatient management of children with type 1 diabetes is clearly one of the most anticipated applications. ■

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