Blood Glucose Monitoring System Accuracy: Why It Matters

For patients with diabetes, achievement of glycemic control must balance between its positive and negative impacts.[1] The positive: Intensive control of blood glucose has been shown to reduce the risk for development and progression of microvascular complications (retinopathy, nephropathy, and neuropathy) of Type 1 and Type 2 diabetes.[2-4] However, the beneficial impacts of intensive glycemic control may be counterbalanced by the negative impacts of the resulting increased incidence of hypoglycemia.

In the Diabetes Control and Complications Trial (DCCT), strict glycemic control in patients with Type 1 (insulin-dependent) diabetes mellitus (T1DM) resulted in a 3-fold increase in the number of hypoglycemic events (62 episodes of severe hypoglycemia per 100 patient-years in the intensive therapy group vs 19 episodes of severe hypoglycemia per 100 patient-years in the conventional therapy group; $P<0.001$).[2] The DCCT Research Group concluded that the goal of intensive therapy in most patients with insulin-treated diabetes should be the maintenance of blood glucose levels as close to normal as possible, but without compromising patient safety.[2]

In patients with Type 2 diabetes mellitus (T2DM), although the frequency of both mild and severe hypoglycemia is generally lower than that in patients with T1DM, the frequency increases as the duration of diabetes increases.[5,6] Another major contributor to the risk for hypoglycemia in patients with T2DM is the type of glucose-lowering medication they have been prescribed. In the UK Prospective Diabetes Study (UKPDS), maintaining tight glycemic control in patients with insulin-treated or sulfonylurea-treated T2DM led to a significant increase in the incidence of severe hypoglycemia.[3] Therefore, hypoglycemia can be an important limiting factor in attaining optimal glycemic control for patients with T1DM and T2DM.[3,7-10]

The burdens of hypoglycemia on patients with diabetes and their health care team

On average, persons with T1DM experience numerous episodes of asymptomatic hypoglycemia and approximately 2 episodes of symptomatic hypoglycemia each week, as well as 1 or more episodes of severe, temporarily disabling hypoglycemia per year.[11,12] In a large global survey (the Global Attitude of Patients and Physicians 2 [GAPP2™]), 80% of people with T2DM who were using insulin had experienced hypoglycemia, with 36% experiencing a hypoglycemic episode within the past 30 days.[13]

Hypoglycemia has a number of negative effects on patients and the health care system.[14,15] **(See Figure 1.)** Hypoglycemia reduces patients' feeling of well-being, and both the severity and frequency of hypoglycemic events are correlated with reduced patient quality of life.[16] Hypoglycemic events can trigger fear and anxiety, disrupt sleep, and impact work and social lives.[16,17] The negative clinical and psychological outcomes of hypoglycemia that can potentially result from intensive treatment aimed at optimal control of blood sugar may further diminish patients' ability and willingness to manage their blood sugar properly.[16]

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Fear of hypoglycemia leads to adverse health consequences

Fear of hypoglycemia on the part of both patients and their health care providers may create a barrier to effective diabetes management and promote compensatory behaviors, such as decreasing insulin and non-insulin medication doses, or not adding needed therapies, in order to avoid future hypoglycemia.[18,19]

Maintaining blood sugar levels with such a "safety margin" (that is, at a higher than recommended level) can lead to a prolonged state of *hyperglycemia*. Following this "margin" strategy leads to elevated hemoglobin A1C (HbA1C) levels, which are associated with an increased risk for diabetic complications and increased health care costs.[20,21] Moreover, the frequency of hypoglycemic events is underreported, because many patients do not inform their health care team about episodes of hypoglycemia.[16]

Economic effects of hypoglycemia

In addition to its effects on clinical outcomes in persons with diabetes, hypoglycemia is associated with substantial economic burdens.[22,23] Data from a large health insurance database was used to estimate the economic impact of hypoglycemic events that resulted in a visit to a health care provider among a cohort of patients with T2DM.[23] The treatment settings included emergency room (ER), inpatient, ER-to-inpatient, and outpatient. Mean direct costs were lowest for a hypoglycemic event treated in the outpatient setting ($285 per event, all drug regimens) and highest for a hypoglycemic event treated initially in the ER and then admitted to the hospital as an inpatient (more than $10,000, all drug regimens).[23]

A study that simulated the additional annual risk for hypoglycemia due to blood glucose monitoring system (BGMS) errors showed that use of

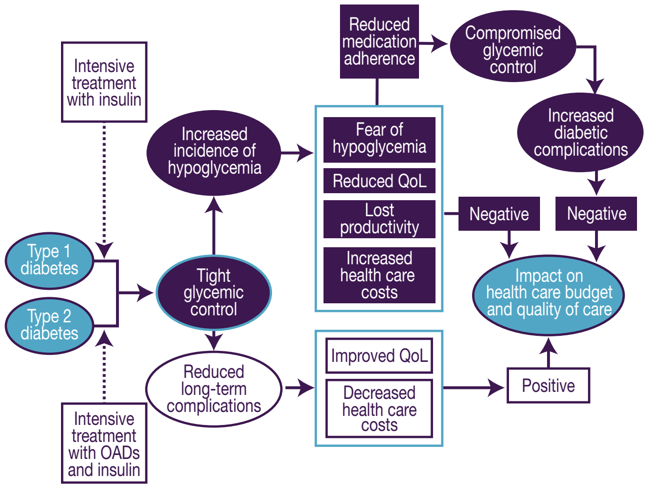

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Figure 1. Impact of hypoglycemia on patients and the health care system.[14] OADs = oral antidiabetic drugs; QoL = quality of life.

more accurate BGMS could help prevent nearly 300,000 additional severe hypoglycemic episodes in patients with T1DM and more than 100,000 severe hypoglycemic episodes in patients with T2DM, with potential savings for the United States (US) health care system of more than $500 million per year.[22] The true cost of hypoglycemia is even higher if its negative effects on good glycemic control over time are considered. **(See Figure 1.)** As patients maintain higher than optimal glucose levels in order to avoid future hypoglycemic events, their risk for long-term complications is increased.[14,19]

Even nonsevere or mild episodes of hypoglycemia can have substantial clinical and economic impacts. In a study of patients with T1DM or insulin-treated T2DM, self-reported, nonsevere hypoglycemic events adversely affected patient well-being, with the most frequent complaints being tiredness/fatigue, feeling less alert, and feeling irritable.[16] **(See Figure 2.)** Slightly more than half of nonsevere hypoglycemic events led to patients reporting loss of work-time, including time away from work as well as lost productivity, where patients were present at their jobs but felt they were not as effective as usual (for example, rescheduling tasks, postponing appointments, or struggling to focus).[16]

A study that investigated the economic consequences of nonsevere hypoglycemia (defined as hypoglycemia not requiring assistance from another individual) for patients with self-reported diabetes and their employers in the US, the United Kingdom (UK), Germany, and France, found that nonsevere hypoglycemia generated a substantial economic burden, due to the frequency of events and lost productivity.[24] Based on the proportion of respondents reporting missed work, multiplied by hourly income and hours missed, the estimated cost per nonsevere hypoglycemic event due to absenteeism ranged from $15.26 to $35.58 (USD) in Germany, $26.43 to $55.16 (USD) in the US, $46.30 to $83.59 (USD) in the UK, and $48.33 to $93.47 (USD) in France.[24]

The role of self-monitoring of blood glucose

Self-monitoring of blood glucose (SMBG) is an important tool for helping patients with diabetes to achieve blood glucose levels as close to normal as possible without developing hypoglycemia.[25] Both patients and their health care providers can use SMBG to assess the effectiveness of their diabetes management plan on glycemic control.[25] For example, in the Structured Testing Program (STeP) study—a large, 12-month, cluster-randomized, multicenter (in the US) clinical trial in primary care—poorly controlled, insulin-naive patients with T2DM who used structured SMBG had significantly greater reductions in mean HbA1C at 12 months (–1.2% vs –0.9%; P=0.04).[26]

Technology-supported behavioral health interventions such as SMBG can encourage more frequent assessment of health parameters, support exchange of health information between patients and the health care team, enable better health decision-making, and encourage positive health behaviors, including self-management and health promotion.[26,27]

Accuracy standards for blood glucose monitoring systems

The 2003 International Organization for Standardization (ISO) 15197 accuracy standard for glucose meters required that 95% of the values obtained be accurate within ±15 mg/dL for blood glucose values <75 mg/dL and within ±20% for blood glucose values ≥75 mg/dL.[28] These standards were updated in 2013 to require that BGMS accuracy be within ±15% of the reference measurement for samples with glucose concentrations ≥100 mg/dL, and ±15 mg/dL when glucose concentrations are <100 mg/dL.[29]

In 2014, the US Food and Drug Administration proposed even smaller allowable errors for BGMS in the hypoglycemic range and fewer errors outside the range **(see Table 1)**; this guidance is still considered a draft.[30]

Even within the boundaries of these standards, considerable differences exist in the performance of commercially available BGMS.[22] Such error patterns over the operating range of BGMS may lead to relevant differences in clinical and economic outcomes. These differences can potentially *increase the risk for not detecting hypoglycemic events when they occur,* and therefore *inadequately identifying and treating them.*[22]

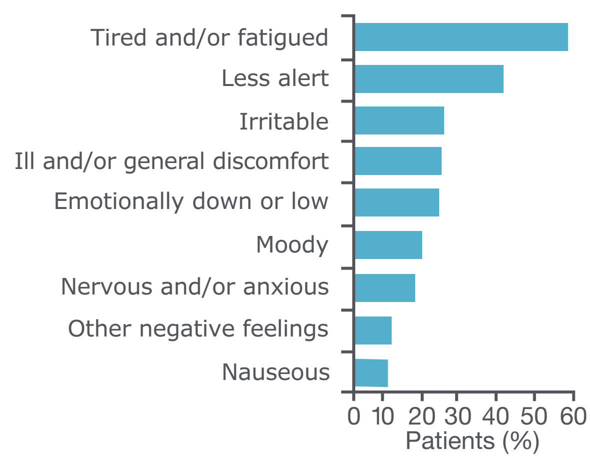

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Figure 2. Patient feelings following a nonsevere hypoglycemic event. Data reported are for the last nonsevere hypoglycemic event reported in the 7-day period.[16]

Table 1. BGMS accuracy standards: past, present, and proposed[28-30]

Standard	Accuracy Criteria	Margin of Error
ISO 15197: 2003[28] (adopted by the FDA 2004; recognized by the FDA until January 2014)	• 95% of results to fall within ±20% of a laboratory reference value for blood glucose concentrations ≥75 mg/dL, and • 95% of results to fall within ±15 mg/dL of a laboratory reference value for blood glucose concentrations <75 mg/dL	Up to **±20%** for blood glucose levels ≥75 mg/dL
ISO 15197: 2013[29] (not adopted by the FDA)	• 95% of results to fall within ±15 mg/dL of a laboratory reference value for blood glucose concentrations <100 mg/dL • 95% of results to fall within ±15% of a laboratory reference value for blood glucose concentrations ≥100 mg/dL, and • 99% of individual glucose measured values shall fall within zones A and B of the Consensus Error Grid	Up to **±15%** for blood glucose levels ≥100 mg/dL
FDA: 2014[30] proposed DRAFT guidance	• 95% of results should be within ±15%, and • 99% of results within ±20% of reference values across the entire glycemic range	Up to **±20%** for blood glucose levels 50-400 mg/dL

FDA = US Food and Drug Administration; ISO = International Organization for Standardization.

Importance of the accuracy of BGMS on blood glucose control

At ±20%, a single blood sample could potentially provide a fairly broad range of blood glucose readings: An actual blood glucose level (that is, the reading that would be obtained under ideal laboratory conditions) of 360 mg/dL could appear as low as 288 mg/dL using a meter with –20% error margin, and as high as 432 mg/dL at an error margin of +20%.

The higher the margin of error of the BGMS, the greater the predicted risk that hypoglycemic events will be missed—and thus inadequately treated. For example, fewer than 1 in 100 hypoglycemic events will be missed via SMBG when the margin of error of the system is ±10%.[31] At a 15% margin of error of the BGMS, the risk increases 4-fold, to 4 in 100 hypoglycemic events missed, and when the BGMS error increases to 20%, the risk for missing a hypoglycemic event rises sharply, to 1 in 10.[31] **(See Figure 3.)** Therefore, a ±20% margin of error could potentially lead a patient to take the wrong course of action to correct his or her blood sugar and result in undercorrection or overcorrection.[31,32]

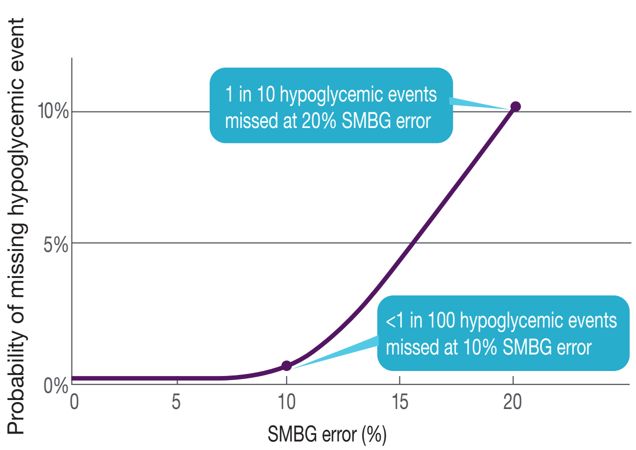

Figure 3. The probability for missing a reference hypoglycemic level of 60 mg/dL as a function of the error in self-monitoring of blood glucose (SMBG).[31]

Commercially available systems can exhibit such differences in performance and may not fulfill minimum accuracy requirements.[22,33]

Meaningful monitoring

Although the ability to maintain good glycemic control depends in part on obtaining accurate readings of blood glucose levels,[34] blood glucose monitoring cannot on its own improve glycemic control. To be useful, the information obtained should be shared with the health care team at and between visits and integrated into the patient's treatment plans.[35] Patients utilize BGMS to detect hypoglycemia and hyperglycemia, titrate insulin dosing, calibrate continuous glucose monitoring devices, and adjust diet and exercise accordingly.[25] Therefore, BGMS are an important tool for helping patients—and their health care providers—to assess the effectiveness of their management plan on glycemic control. The American Diabetes Association considers SMBG to be an integral part of diabetes management for patients with either T1DM or T2DM.[25]

The 2016 consensus statement on outpatient glucose monitoring from the American Association of Clinical Endocrinologists and American College of Endocrinology encourages "meaningful monitoring," which is the idea that monitoring should be used in a way that informs decisions on disease management.[35] Meaningful monitoring implies that, in order to be useful, the information obtained via SMBG must be understood by the patient, communicated to the patient's health care team, and then integrated into self-management plans for maintaining glycemic control.

Education is an essential part of clarifying the relationship between specific glucose data and medication, as well as other therapeutic interventions. Health professionals should educate patients about interpreting and using SMBG data in a way that helps them identify glucose patterns and responses to various components of their therapy, enhance patients' ability to self-adjust their therapy between office visits, and help them decide when to seek medical assistance.[35]

Clinical practice guidelines from all of the major diabetes organizations recommend that patients with T1DM monitor their blood sugar on a routine basis.[35] For patients with T2DM, meaningful monitoring should be individualized by the physician and the health care team in partnership with the patient, depending on the patient's risk for hypoglycemia. Assessment of this risk is based on factors such as prior history, the patient's own awareness of when he or she is experiencing an episode of hypoglycemia, and current therapy (for example, whether the patient is receiving medications that increase the risk for hypoglycemia, such as insulin, sulfonylureas, or glinides).[35] **(See Table 2.)** Meaningful SMBG can help empower patients to play a more active role in managing their diabetes and can help maximize the efficacy and safety of all glucose-lowering therapies.

Technology and meaningful monitoring

Recently, technology-supported mobile applications (apps) have aided meaningful monitoring by permitting more frequent and more convenient assessment of health parameters, supporting the exchange of health information between patients and health care providers, enabling informed health decision-making, and encouraging positive health behaviors.[36] The pooled results of a meta-analysis of 11 studies that evaluated computer-based diabetes self-management interventions in adults with T2DM found that there was a small but statistically significant beneficial effect on HbA1C (–0.2%; $P=0.009$) in the intervention groups; the effect on HbA1C was greater among patients in the subgroup using mobile phone interventions (–0.5%; $P<0.00001$).[37]

Table 2. Clinical situations that may require greater glucose monitoring accuracy[35]

Patients requiring the highest possible accuracy in glucose monitoring
• History of severe hypoglycemia
• Hypoglycemia unawareness
• Pregnancy
• Infants and children receiving insulin therapy
• Patients at increased risk for hypoglycemia, including:
— Patients receiving basal insulin
— Patients receiving basal bolus insulin therapy with multiple injections per day
— Patients receiving insulin secretagogues
— Patients with irregular schedules, skipped or small meals, vigorous exercise, travel between time zones, disrupted sleep schedules, shift work
• People with occupational risks that enhance possible risks from hypoglycemia (for example, involving driving or operating hazardous machinery)

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Why BGMS accuracy matters

The fear of hypoglycemia, its clinical and psychological impacts, and its substantial associated "hidden" costs, all have major negative effects on the overall burden of diabetes. Patients' use of BGMS that provide accuracy close to laboratory reference values—especially at blood glucose levels for which the incorrect reading is most likely to cause a clinical error—may help reduce this burden.[22] Patients with diabetes rely on accurate BGMS to detect and properly manage hypoglycemia, titrate medication doses, adjust diet and activity, and improve overall decision-making in managing their disease.[25] Accurate BGMS play a role in ensuring that patients and their health care providers have confidence in their blood sugar readings and can trust that those results will help the patient attain optimal glycemic control.

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