Possible Impacts of New Accuracy Standards of Self-Monitoring of Blood Glucose

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Abstract

Self-monitoring of blood glucose (SMBG) was an integral part of reduction of complication rates in the landmark Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes. However, the accuracy and standardized reporting of SMBG devices remains a key concern, with the 2003 version of International Organization for Standardization (ISO) 15197 standards allowing for 5 % of readings to fall outside of the acceptable ranges. A recently revised 2013 version of the ISO 15197 standards includes stricter accuracy standards, with a 36-month transition period recommended before compliance becomes mandatory. These new accuracy standards will have implications not only for manufacturers of currently available and future devices but also for the end-users, who may face rising costs and necessary measures to improve patient error rates associated with SMBG in routine clinical practice.

Keywords

Type 1 diabetes, Type 2 diabetes, self-monitoring of blood glucose, accuracy, performance, ISO 15197

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Recently, the International Diabetes Federation (IDF) estimated 371 million individuals are living with diabetes worldwide, including 50 % who remain undiagnosed. 1 The prevalence of diabetes is increasing in every country, and is estimated to cross the half-billion mark by 2030. 2 In 2012, worldwide diabetes healthcare expenditure was estimated at $471 billion, 3 and in the US was estimated at $245 billion (a 41 % increase over the past 5 years). 3

Intensive diabetes management is essential for preventing or delaying micro- and macrovascular complications of this disease. According to the Diabetes Control and Complications Trial (DCCT), achieving better glucose control was facilitated by frequent self-monitoring of blood glucose (SMBG). 4 The DCCT found that intensive therapy of Type 1 diabetes (insulin administered ≥3 times/day by injection or external pump along with SMBG performed ≥4 times/day) significantly reduced the risks of new-onset retinopathy by 76 % and slowed retinopathy progression by 54 % compared with conventional therapy (i.e. one to two insulin injections with daily SMBG or urine testing). Longer-term follow-up (mean of 17 years) of DCCT patients in the Epidemiology of Diabetes Interventions and Complications study also showed significant reduction of macrovascular events among patients who had received intensive therapy. 5 Despite documented long-term success of tight glycemic control in Type 1 diabetes, 4 real-world self-management remains poor, as illustrated by low daily (39 %) and routine (67 %) rates of SMBG in a Danish-British survey of >1,000 patients with Type 1 diabetes. 6 In a recent analysis of the T1D Exchange Clinic Registry, which included >13,000 pediatric patients aged <20 years with a history of Type 1 diabetes for ≥1 year, most participants failed to attain specified A1c targets (<7.5 % to <8.5 %); however, achievement of this goal was highest among the youngest patients (64 % for patients aged 1 to <6 years versus 43 % for ages 6 to <13 years and 21 % for ages 13–20 years). 7 A second analysis from the T1D Exchange Clinic Registry demonstrated a direct relationship between SMBG frequency and A1c values, regardless of age or use of insulin pump versus injection. 8, 9

In contrast to the Type 1 diabetes population, the role of SMBG for patients with noninsulin-treated Type 2 diabetes is highly controversial, promoting substantial discussion, debate, and the conduct of numerous prospective and retrospective studies as well as meta-analyses to address this matter. 10–27 Overall, randomized controlled trials have yielded mixed results as to whether SMBG improves glycemic control in noninsulin-treated patients with Type 2 diabetes. 16, 21–27 Systematic reviews and meta-analyses have demonstrated a consistently small (about 0.2–0.3 %) but statistically significant SMBG-derived improvement in A1c control among patients with Type 2 diabetes; however, the clinical relevance of such a modest improvement has been questioned, especially from a cost–benefit standpoint. 11, 12, 28, 29 In a US cost-effectiveness model, 40-year risks for 14 of 16 evaluated types of complications favored the use of SMBG (one to three times/day versus no SMBG) in patients with Type 2 diabetes receiving oral antidiabetic therapy. 15
Current American Diabetes Association (ADA) recommendations call for frequent SMBG for patients on multiple-dose insulin or insulin pump therapy. Per expert consensus or clinical experience of the panel, when SMBG is used as a component of broader education for patients administering less frequent insulin injections or non-insulin therapies, it may be helpful for guiding treatment decisions and/or patient self-management.

Personal (‘realtime’) continuous glucose monitoring (CGM) was developed with the goal of identifying both hyperglycemic and hypoglycemic trends, allowing for timely therapeutic adjustments. The first US Food and Drug Administration (FDA) approval of a realtime CGM device was granted in 1999 (GlucoWatch Biographer, Cygnus Inc, Redwood City, CA, which had a number of shortcomings and is no longer manufactured), with several other personal CGM devices (e.g. Navigator, Abbott Diabetes Care, Alameda, CA; Medtronic, Northridge, CA; DexCom, San Diego, CA) subsequently approved. The ADA 2013 clinical practice guidelines recognize the potential for CGM plus intensive insulin therapy to reduce A1c in selected adults (aged ≥25 years) with Type 1 diabetes, citing the highest level of evidence (i.e. from well-conducted, generalizable, randomized controlled trials). Lower-level evidence suggests CGM may also benefit younger patients, and expert consensus supports a supplemental role in patients with hypoglycemia unawareness and/or frequent hypoglycemia.

Multiple reports demonstrate incidents of dangerous overnight hypoglycemia and postprandial hyperglycemia detectable with CGM, but normally missed by SMBG. Given calibration of currently available CGM systems is reliant on SMBG, it is important to note that CGM is currently approved as an adjunctive device only. The dependency of CGM technology on SMBG makes the accuracy of SMBG values of even greater importance as CGM becomes standard of care.

**Accuracy of SMBG Devices**

Traditionally, the concept of SMBG accuracy captures how close an average of readings is to a reference value, not how closely or how many of the individual readings equate to the reference value. A number of accuracy standards have been proposed over the years. The ADA proposed standards for SMBG device accuracy as early as 1987, when they recommended total error (i.e. analytical plus user error) be <10% for 100% of glucose concentrations 30 to 400 mg/dL. In 1996, with recognition of the crucial role of SMBG in the improved outcomes achieved in the DCCT, the recommendation was revised to support a maximum analytical error <5%. Subsequently, a collaborative effort involving the International Organization for Standardization (ISO), international regulatory authorities, healthcare providers, and SMBG manufacturers established minimum accuracy standards for SMBG devices (known as the ISO 15197 criteria), originally released in 2003 and recently updated for 2013 (see Table 1). The major critique of the ISO 15197:2003 guidelines, which had been adopted by the FDA and other regulatory authorities, is that the 5% (or one in 20) threshold was too high and therefore allowed for too many large, medically unacceptable errors. In the 2013 revision, this matter was addressed by...
a new requirement to address outliers, requiring that 99 % of readings fall within zones A and B of the survey-derived Consensus Error Grid for Type 1 diabetes (see Figure 1).41

There has been an increasing amount of published literature characterizing the relative accuracy of commonly used SMBG43–50 and CGM systems. One study evaluated the accuracy of 27 SMBG devices according to the ISO 15197:2003 criteria and found that >40 % of evaluated systems yielded results for concentrations ≥75 mg/dl that failed to meet the requirement of ≥95 % concentrations within ±20 % of the reference method.43 A second large study found seven of 34 (21 %) assessed SMBG failed to meet the ISO 15197:2003 criteria.49

In March 2010, the FDA/Center for Devices and Radiological Health held a public meeting on blood glucose monitors, prompted by ongoing questions from the clinical and patient communities surrounding acceptability of accuracy standards and requests for stricter FDA performance standards. This renewed attention on SMBG device accuracy stems from concerns about detecting hypoglycemia and the failure of achieving A1c targets, and other factors such as an emerging role for SMBG in hospital intensive care units. The FDA meeting conclusions highlighted the need for better analytical and clinical performance of SMBG devices, and methods to address the ‘human factor errors’ known to influence SMBG readings.53 As one of the specific outcomes of this meeting, it was anticipated that the FDA would move away from the ISO 15197:2003 criteria in favor of tighter standards.

The revised criteria also do not address the different accuracy needs of various patient groups. For example, noninsulin-treated patients may use SMBG as a general gauge (e.g. to periodically track their overall progress), while women with gestational diabetes or some hospitalized patients require tighter glycemic control and more accurate SMBG monitoring.42,53

The new ISO 15197:2013 standards are not the only accuracy standards that have been proposed for SMBG devices. In October 2011, a group of 45 invited clinicians participated in a closed-door meeting at the 11th Annual Diabetes Technology Meeting to discuss possible standards. They proposed a less stringent baseline set of guidelines for devices (95 % of readings within ±10 mg/dl below 75 mg/dl and ±15 % above 75 mg/dl, with <2 % of readings being >±15 mg/dl below 75 mg/dl or >±15 % above 75 mg/dl) and a method of grading the accuracy of meters for hypoglycemic, euglycemic, and hyperglycemic readings that would be accessible to patients,54 e.g. a meter with an accuracy of ≤5 mg/dl for readings between 30 to 75 mg/dl would receive an ‘A’ and an accuracy of ≤10 mg/dl a ‘B’ rating.54 This information, currently unavailable to patients, would likely foster a competitive market for meters and encourage continuing improvement in accuracy.

Impact of Tighter SMBG Device Accuracy on Diabetes Care

With recognition that many commercially available SMBG devices were developed based on original ISO 15197:2003 standards, the ISO advised that a 36-month transition period be instituted before requiring mandatory compliance with the revised 2013 standards.41 Clearly, tighter standards will pose challenges for device manufacturers, particularly given the gamut of SMBG result-influencing factors (see Table 2), many of which cannot be controlled by manufacturers; thus, developing SMBG meters with continually improving accuracy may not necessarily be realistic.54

One of the driving factors behind the new ISO 15197:2013 criteria is the notion that better performing SMBG devices will result in more accurate insulin dosing, which should translate into better patient outcomes.41 However, although this rationale is logical, there currently is no head-to-head evidence demonstrating that differences in analytical accuracy between SMBG meters are associated with differences in clinical outcomes in Type 1 or 2 diabetes.55

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Recommendations for other SMBG aspects should also be considered. Minimization of patient error could be addressed, e.g. with individually wrapped strips to maintain consistency and eliminate interference from humidity or high temperatures, which could effect SMBG readings.36,55 Healthcare providers and patients could also benefit from standardized meter reporting, similar to electrocardiogram readings from different manufacturers. Currently, every meter download looks different, and some reports are difficult to understand or have limited applicability. The need for standardized reporting and data analysis is highlighted in a summary report.

Table 2: Factors Influencing the Accuracy of SMBG Devices34,36,55

<table>
<thead>
<tr>
<th>Strip Factors</th>
<th>Patient Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lot-to-lot variability</td>
<td>• Miscoding of the device (ameliorated by some newer devices that avoid coding)</td>
</tr>
<tr>
<td>• Changes in enzyme coverage</td>
<td>• Variations in hematocrit</td>
</tr>
<tr>
<td>• Reduction of the mediator for electrochemical blood glucose strips</td>
<td>• Patient error (e.g. improper technique, improper device, or test strip storage, and erroneous reading or interpretation of results)</td>
</tr>
<tr>
<td>• Improper storage (including high temperature or humidity or storage with an open vial)</td>
<td>• Contaminants from poor hand washing</td>
</tr>
<tr>
<td>• Relatively short shelf-life, with expiration dates generally ~2 years under ideal conditions</td>
<td>• Interfering physiologic substances (e.g. triglycerides, oxygen, and uric acid)</td>
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</table>

<table>
<thead>
<tr>
<th>Physical/Environmental Factors</th>
<th>Pharmacologic/Treatment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Influence of high and low temperatures</td>
<td>• Medications interfering in electrochemical glucose oxidase systems (e.g. acetaminophen, L-dopa, tolazamide, and ascorbic acid)</td>
</tr>
<tr>
<td>• Influence of high altitude</td>
<td>• Medications interfering with glucose dehydrogenase (e.g. icodextrin, which is a component of some peritoneal dialysis fluids)</td>
</tr>
<tr>
<td>• Oxygen concentration for glucose oxidase biosensor strips</td>
<td>• Oxygen therapy</td>
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Diabetes Blood Glucose Monitoring
from an expert panel meeting in March 2012, and a letter from the FDA. Moreover, from an end-user perspective, the relative importance of inherent device accuracy versus other features, e.g. durability/ease-of-use, will vary greatly depending on intended use. Increased accuracy also needs to be balanced against increased cost. It is reasonable to anticipate that many patients will resist switching to a new meter, particularly if there is increased monetary or nonmonetary cost (e.g. greater discomfort, larger size of a given sample, or the monitor itself). Additionally, use of accuracy as a primary criterion for SMBG device selection among patients and caregivers may be confounded by the absence of accurate data/products on package packaging. Finally, cost is a major healthcare concern, although diabetes drugs, devices, and supplies account for only 28% of associated costs. A notification from Medicare/Medicaid indicated that as of 2014 all strips would be reimbursed at only ~$11/box of 50 lancets and strips, which is significantly lower than current reimbursement rates. If the new ISO 15197:2013 standards lead to significant cost increases their adoption might be poor.

The ongoing progress of SMBG’s has culminated in many unanswered questions and directions for future research. Tighter standards should lead to more accurate SMBG devices; however, patient-focused efforts are required to improve barriers that will not be overcome by even the most accurate meters, including poor adherence to prescribed SMBG frequency and patient error in storage, sampling technique, and reading and interpretation results. Standardization reporting and reduced costs may be mandatory with increasing healthcare costs.