

Continuous Glucose Monitoring: A Perspective on Its Past, Present, and Future Applications for Diabetes Management

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The transition from urinary glucose measurement to more sophisticated self-monitoring of blood glucose (SMBG) systems in the 1970s and 1980s dramatically changed the approach to and understanding of diabetes management (1). Innovations in the design and technology of portable blood glucose meters have become integral to the success of intensive treatment of both type 1 and type 2 diabetes, and the outcome of this treatment has led to a tremendous decrease in the development of long-term micro- and macrovascular complications (2–4). However, intensive insulin therapy has its limitations, including increased frequency of hypoglycemia and the need for frequent SMBG testing.

In the past decade, continuous glucose monitoring (CGM) technology has evolved into a novel tool to support diabetes management. Unlike conventional glucose meters, which provide a snapshot of the blood glucose value at the time of testing, CGM provides semi-continuous information about glucose levels. It does this indirectly, by extrapolating blood glucose levels from interstitial fluid glucose via an algorithm. Importantly, CGM allows users to make decisions regarding their day-to-day diabetes management using real-time glucose trends. Along with this information, CGM systems provide customizable hypo- and hyperglycemia alarms and display trends of the rate of change of glucose levels. Most recently, CGM systems

have been integrated with insulin pumps and are being used in artificial pancreas clinical trials. In this article, we discuss the clinical benefits of CGM; its challenges, including accuracy and user experience; and its present and future role in the management of diabetes.

Clinical Benefits of CGM

Numerous studies have explored whether sustained use of CGM offers clinical benefits in individuals with diabetes. Randomized, multicenter clinical trials have shown improved glycemic control in adults with type 1 diabetes using CGM compared to those using SMBG and a reduction in the time spent in hypoglycemia with concomitant improvement in A1C for those using CGM technology (5–10). Even in patients with type 1 diabetes whose diabetes was well controlled at baseline with an A1C <7%, CGM reduced the time spent out of range (≤ 70 or > 180 mg/dL) with stable A1C levels after 6 months (11). In patients with type 2 diabetes, CGM has also been shown to improve A1C and reduce the time spent outside of glycemic targets, with the largest reduction in patients with a baseline A1C $> 9\%$ (12,13).

Adherence to and frequency of CGM use over time has been a particularly important aspect of the associated reduction in A1C. More frequent CGM use in all age-groups has been associated with greater A1C reduction from baseline to 6 months (14). Both the Juvenile Diabetes

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Research Foundation Continuous Glucose Monitoring Randomized Clinical Trial and the Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 1 trial showed that lower A1C levels were observed in patients who used CGM $\geq 60\%$ of the time (5,15). The STAR 3 trial showed that increased frequency of sensor use was associated with greater A1C reduction, and sensor use $>80\%$ of the time resulted in a doubling of the effect (16).

CGM Patient Selection and Clinician Education

Important considerations need to be made when recommending CGM therapy. As reported in the American Association of Clinical Endocrinologists (AACE) 2010 consensus statement on CGM, appropriate candidates include individuals with type 1 diabetes who have hypoglycemia or hypoglycemia unawareness and who have an A1C above their target (17). In 2011, the Endocrine Society released its first CGM guidelines and recommended the use of CGM in adults with type 1 diabetes who can demonstrate that they can use these devices on a nearly daily basis (6–7 days per week) (18). Similarly, in a white paper based on a 2015 CGM summit, the American Association of Diabetes Educators (AADE) stated that CGM may be appropriate for any person with diabetes who is willing to wear a CGM device, regardless of age, diabetes type, or duration of diabetes (19). Recently, a 2016 AACE CGM consensus conference suggested that the use of CGM may be especially beneficial for type 1 diabetes patients who are >65 years of age with comorbidities or at risk for severe hypoglycemia, as well as for patients with diabetic chronic kidney disease (20). Additionally, it suggested that the benefits of CGM therapy also may apply to insulin-treated individuals with type 2 diabetes, as well as pregnant women with diabetes, although more studies are needed in these populations (20).

In its 2015 CGM summit white paper, AADE outlined the benefits of CGM therapy in identifying glycemic excursions, characterizing the effects of physical activity and high-glycemic index meals on glucose levels, and mitigating hypoglycemia frequency and severity via alerts and alarms for impending hypoglycemia (19). Most importantly, AADE emphasized the need to adequately select and train patients who wish to use CGM technology. Training is essential to understanding appropriate calibration of the device and factors that can influence sensor accuracy, the lag time between CGM values and SMBG values, and the meaning of glucose trend information (i.e., rising or falling glucose levels). Setting up individualized alarms and alerts is of paramount importance to prevent alarm fatigue; similarly, it is important to train patients to monitor for skin problems, allergic reactions, sensitivity caused by tape (e.g., itching, redness, or hives), or poor CGM sensor adhesion that may affect long-term use of CGM (19).

The successful adoption of CGM technology also greatly depends on clinician education. As described in the 2016 AACE consensus, CGM training programs should be available to all health care providers involved in the diabetes management of patients using CGM therapy. Training should address not only knowledge of the available systems to effectively deliver CGM patient education, but also information regarding how to interpret the CGM data reviewed during clinical visits (20). Presently, several downloadable reports are available, requiring brand-specific software. The availability of a downloadable report that is standardized for all CGM device brands would greatly facilitate data interpretation for both patients and clinicians (20).

Accuracy of CGM Systems

Subcutaneous CGM sensors measure glucose concentration in the body's interstitial fluid and use advanced al-

gorithms to extrapolate blood glucose levels from these readings. Because CGM does not provide a direct measurement of blood glucose, intermittent calibration with capillary glucose measurements is needed. Although this calibration helps, it is noteworthy that a physiological time lag of glucose transport from the intravascular to the subcutaneous interstitial space is a major determinant of sensor accuracy (21). Studies have demonstrated that this time lag is ~ 7 – 8 minutes in the overnight fasted state in adults with type 1 diabetes (21) and ~ 5 – 6 minutes in healthy individuals without diabetes (22). Most recently, the time lag of interstitial fluid sensors was estimated to be as little as 5 – 6 minutes in adults with type 1 or type 2 diabetes (23). Understanding the physiological mechanisms underlying CGM technology, such as the time lag of glucose transport, allows better refinement of the predictive algorithms used in the alarm and trend features, as well as in closed-loop systems.

Another important factor in determining sensor accuracy is the calibration made with blood glucose measurements. Therefore, the accuracy of the SMBG system used for calibration plays an important role in determining CGM sensor accuracy such that the more accurate the glucose meter used to calibrate a CGM device is, the more accurate the initial calibration data will be. Historically, the International Organization for Standardization (ISO) 15197 standard has been used to evaluate the accuracy of SMBG systems. The most recent version (2013) requires at least 95% of individual meter results to fall within ± 15 mg/dL for blood glucose concentrations <100 mg/dL and within $\pm 15\%$ for blood glucose concentrations ≥ 100 mg/dL (24). In 2014, the U.S. Food and Drug Administration (FDA) published a draft guidance document for the premarket evaluation of SMBG devices that stipulates that 95% of all SMBG results should be within

$\pm 15\%$ of the reference measurement across the entire measuring range of the device and that 99% of results are within $\pm 20\%$ (25). Although many glucose meters meet the ISO 15197 standard and the new FDA criteria, some do not (26–29). Some studies have demonstrated that only 14–67% of SMBG devices meet the 2013 ISO standard (30). This poses challenges to CGM calibration and therefore to the accuracy of the CGM system as a whole.

CGM accuracy metrics have been categorized into two subtypes: numerical and clinical (31). Numerical accuracy traditionally has been defined by analyzing single glucose pairs comparing the value obtained from a monitoring device to a standard reference value. These analyses include mean absolute relative difference (MARD), correlation coefficients, and the ISO criteria and have been used to evaluate the accuracy of SMBG systems (31). Some metrics, such as MARD values, which compare the device values to matched reference glucose measurements, are thought to allow a better comparative assessment of multiple systems' accuracy rather than the binary method as defined by ISO 15197. The smaller the MARD value, expressed as a percentage, the more accurate the device is when compared to the reference glucose value. However, when applied to CGM systems, the above metrics may not fully reflect the additional clinical utility provided by the collection of continuous data regarding glucose fluctuations and rate of change in glucose level.

CGM data are much more complex because of their continuous nature, with each CGM glucose value related in time and direction to the preceding value. Therefore, the numerical metrics described above do not fully measure the clinical accuracy of CGM devices. Traditionally, the clinical accuracy of SMBG devices has been defined by error grid analysis (EGA), which not only takes

into account the absolute and relative differences between the device reading and a reference value, but also addresses the clinical significance of this difference. EGA plots the values obtained by the monitoring device against the reference values into five zones, each of which has clinical significance based on varying degrees of accuracy and inaccuracy of glucose estimations, which would lead to either correct or incorrect treatment decisions (32). Similarly, CGM accuracy has been evaluated with the continuous glucose–error grid analysis (CG-EGA), which adds rate and direction of change to single-point glucose accuracy (33,34). CG-EGA analyzes pairs of reference and sensor readings as a bi-dimensional time series that takes into account physiological time lags (34). Although many different methods of measuring CGM accuracy have been described, the FDA currently uses MARD values, hypoglycemia and hyperglycemia detection and missed detection rates, true and false alert rates, and the accuracy of sensor glucose rate of change data compared to a reference rate of change to determine approval of new devices.

CGM accuracy has significantly improved over time, from very poor performance of the initial CGM systems, which had MARD values $>20\%$, to the newest-generation devices, which have MARD values $<10\%$. Since FDA approval of the first CGM device in 2001, newer generations have demonstrated significantly improved accuracy of glucose sensors at all glucose ranges. A comparison study of three CGM systems (FreeStyle Navigator, Abbott Diabetes Care, Alameda, Calif.; G4 Platinum, Dexcom, San Diego, Calif.; and Enlite, Medtronic MiniMed, Northridge, Calif.) reported MARD values of 12.3 and 10.8%, respectively, for the Navigator and G4 Platinum, compared to a MARD value of 17.9% for the Enlite (35). Another comparison of two CGM systems under both clinical research

conditions and everyday home use demonstrated MARD values of 13.6 and 16.6% for clinical research use for the Dexcom G4 Platinum system and the Medtronic Enlite system, respectively, and 12.2 and 19.9% for home use of the devices, respectively (36). As with SMBG systems, MARD values in the hypoglycemic range <70 mg/dL were higher (17.6% for the G4 Platinum and 24.6% for Enlite) (36). However, the G4 Platinum (software 505) CGM system reported improved accuracy in the hypoglycemic range compared to previous-generation devices, with an overall MARD of 9% at all glucose ranges (23,37). Currently, the Dexcom G5, which uses new software and was recently approved by the FDA, is the most accurate personal CGM on the market (Table 1). Research targeting CGM calibration algorithms is ongoing, with the goal of further improving accuracy, especially in the hypo- and hyperglycemic ranges, and this research continues to show promising results (38).

Although CGM devices are currently approved by the FDA for adjunct use only and require SMBG for insulin dosing decisions, the new data suggest that the considerable improvements in CGM accuracy in the latest generation of sensors could allow implementation of CGM systems as a stand-alone tool for glucose monitoring. An in-silico study of CGM, insulin pump, and SMBG data found that using CGM rather than SMBG for insulin dosing decisions was feasible at MARD values $\leq 10\%$ and that further accuracy improvement did not substantially improve glycemic outcomes (39).

Clinical Experience and Barriers to CGM Use

Despite a growing body of evidence of the clinical benefits of CGM and the continually improving accuracy of CGM devices, this technology is not yet widely used. The nationwide T1D Exchange clinic registry, which includes 76 endocrinology practices and

TABLE 1. Personal CGM Devices

Device	Calibration	Approval	Interference	Duration of Use (days)	MARD (%)
Medtronic Enlite* (51)	At least once every 12 hours; optimal accuracy with three to four calibrations per day	For patients ≥ 16 years of age	Acetaminophen may cause false elevation in sensor glucose readings	6	13.6 (52)
Dexcom G4 Platinum (53)	At least once every 12 hours	For patients ≥ 2 years of age	Acetaminophen may cause false elevation in sensor glucose readings	7	10.8 (35)
Dexcom G5 Mobile (54)	At least once every 12 hours	For patients ≥ 2 years of age	Acetaminophen may cause false elevation in sensor glucose readings	7	9 (23)

*Integrated with MiniMed 530G insulin pump.

>26,000 enrolled subjects with type 1 diabetes, recently reported 11% CGM use overall, compared to 62% use of insulin pump therapy across all age-groups (40). In addition, documented CGM use tends to decrease over time, although less so in adult patients (10). There may be multiple reasons why this technology is not embraced in clinical use to the same degree as other technologies such as insulin pump therapy. Some obstacles identified include cost and reimbursement issues, clinicians' unwillingness to learn or implement new technology, and user factors such as alarm fatigue and perceptions of inaccuracy or interference with daily life.

Several studies of quality-of-life factors indicate that individual experiences with CGM can be quite variable (41,42). In a large survey of 877 CGM users with the Dexcom Seven Plus System, most (>80%) reported an improved sense of control over diabetes and confidence in the management and avoidance of hypoglycemia (41). In the same survey, satisfaction with device accuracy was an independent predictor of greater perceived control over diabetes, perceived hypoglycemic safety, and interpersonal support. Conversely, equipment malfunction and interference with daily life were major reasons reported by patients for sensor discontinuation (42,43). In a qualitative analysis of 100 patient narratives (50 adults with type 1 diabetes and 50 caregivers of children with type 1 diabetes), several barriers to CGM use were identified, despite overall positive experiences noting improved glycemic control, diet and exercise management, quality of life, and physical and psychological well-being. Among the barriers were concerns about accuracy and reliability, financial issues, and the attitudes of health care professionals (44). Because many of the studies reporting adherence data were performed with earlier-generation devices, we may expect that adherence rates and

user experiences will improve over time.

Although CGM alarms are a crucial factor leading to the reduction of hypoglycemia, excessive device alarms can also be erroneous, too frequent, or unnecessary, and therefore lead to alarm fatigue (6,45). Many patients report alarm fatigue as a major barrier to CGM use and adherence (42,43). Earlier studies of first-generation CGM technology found that up to 30% of all alarms, and up to 50% of alarms for hypoglycemia, may have been false (46,47). Although newer CGM systems have improved accuracy, alarm fatigue and perceptions of inaccuracy of the alarms may make users less likely to respond to hyper- or hypoglycemia. On the other hand, confidence in the device accuracy can result in increased use of CGM (42,48). Hopefully, as the technology advances and accuracy continues to improve, user acceptance and confidence in the utility of CGM will increase as well.

Device Connectivity

Continuing progress in interconnectivity between blood glucose monitoring devices, including CGM and SMBG devices, and insulin pumps offers much promise for the near future. Sensor-augmented insulin pump therapy has been shown to result in greater A1C reductions than multiple daily insulin injections without an increase in the frequency or severity of hypoglycemic events (16). Integration of CGM technology with insulin pumps, such as the Medtronic MiniMed 530G with Enlite, has allowed implementation of a threshold-suspend feature, which allows suspension of insulin delivery for up to 2 hours in the setting of hypoglycemia and has been shown to reduce nocturnal hypoglycemic events (49).

Improved communication between devices can further enhance the patient experience. For example, direct communication via Bluetooth technology between the CGM transmitter in the Dexcom G5 system and

a mobile phone application without the need for a separate receiver has allowed the integration of multiple devices. These integrated devices can also communicate with web-based diabetes management software. The Dexcom SHARE mobile application allows CGM data to be shared in real time with additional users such as family or friends, who can also receive alerts for hypo- and hyperglycemia, potentially increasing interpersonal support for patients with diabetes. Medtronic's MiniMed Connect similarly allows the uploading of glucose data to a phone application and the ability to share this information with others via a web-based portal. Such patient-centered applications have allowed for home downloading and analysis of glucose data, as well as sharing that information with health care providers. Highlighting the need for this type of technology, other do-it-yourself applications such as the Nightscout Project (50) have been designed by patients and their family members to take advantage of FDA-approved CGM devices and upload glucose data to a web-based server to allow remote monitoring by concerned family members.

Conclusion

CGM has continued to evolve and advance as a novel tool for diabetes management. Despite its documented clinical benefits, this technology is not yet widely used. Although its accuracy has significantly improved in the past decade, CGM is currently approved in the United States only for adjunct use, and barriers to its use include such factors as alarm fatigue and patient perceptions of poor accuracy or interference with daily life. New data suggest that the considerable improvement in CGM sensor accuracy could potentially allow its implementation as a stand-alone tool to help guide insulin dosing decisions. The T1D Exchange is currently conducting a randomized clinical trial funded by the Leona M. and Harry B. Helmsley Charitable Trust to com-

pare CGM with and without routine SMBG in adults with type 1 diabetes, with the goal of obtaining more data about the efficacy and safety of CGM for this purpose. The results of this study, as well as data documenting enhanced CGM accuracy, may have a great impact on the future use of CGM as an independent method of glucose monitoring for individuals with diabetes.

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Duality of Interest

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