DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Supplement 2, 2016

DOI: 10.1089/dia.2015.0417

REVIEW

Continuous Glucose Monitoring: A Review of Successes, Challenges, and Opportunities

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Abstract

Continuous glucose monitoring (CGM) provides information unattainable by intermittent capillary blood glucose, including instantaneous real-time display of glucose level and rate of change of glucose, alerts and alarms for actual or impending hypo- and hyperglycemia, ''24/7'' coverage, and the ability to characterize glycemic variability. Progressively more accurate and precise, reasonably unobtrusive, small, comfortable, user-friendly devices connect to the Internet to share information and are *sine qua non* for a closed-loop artificial pancreas. CGM can inform, educate, motivate, and alert people with diabetes. CGM is medically indicated for patients with frequent, severe, or nocturnal hypoglycemia, especially in the presence of hypoglycemia unawareness. Surprisingly, despite tremendous advances, utilization of CGM has remained fairly limited to date. Barriers to use have included the following: (1) lack of Food and Drug Administration approval, to date, for insulin dosing (''nonadjuvant use'') in the United States and for use in hospital and intensive care unit settings; (2) cost and variable reimbursement; (3) need for recalibrations; (4) periodic replacement of sensors; (5) day-to-day variability in glycemic patterns, which can limit the predictability of findings based on retrospective, masked ''professional'' use; (6) time, implicit costs, and inconvenience for uploading of data for retrospective analysis; (7) lack of fair and reasonable reimbursement for physician time; (8) inexperience and lack of training of physicians and other healthcare professionals regarding interpretation of CGM results; (9) lack of standardization of software methods for analysis of CGM data; and (10) need for professional medical organizations to develop and disseminate additional clinical practice guidelines regarding the role of CGM. Ongoing advances in technology and clinical research have addressed several of these barriers. Use of CGM in conjunction with an insulin pump with automated suspension of insulin infusion in response to actual observed or predicted hypoglycemia, as well as progressive refinement of closed-loop systems, is expected to dramatically enhance the clinical utility and utilization of CGM.

Introduction

When continuous glucose monitoring (CGM) first became commercially available in the year 2000 its measurement error was more than ±20%.[1] Today, overall measurement error has been reduced by twofold (±10%),[2–5] and accuracy continues to improve. Size, weight, complexity, and cost of CGM sensors/devices have decreased, whereas the duration of use, specificity, user-friendliness, user interface and displays, data management, and software for data analysis have improved. Numerous studies have demonstrated clinical benefits in multiple patient populations—pediatrics, adolescents, and adults, type 1 and type 2—with various levels of glycemic control at baseline.[6–12] Benefit is directly proportional to frequency of use.[6–12] The effectiveness of CGM can be synergistic with the benefits associated with insulin pumps.[10] Use of CGM is generally associated with an improvement in the hemoglobin A1c (HbA1c) level and/or reduction in the risk of hypoglycemia, depending on the baseline characteristics of the patient population.[10] Econometric studies using accepted methodology indicate that the use of CGM can be cost-effective to society in terms of the ratio of quality-adjusted life-years saved relative to costs,[13–15] largely due to a reduced risk of hypoglycemia.

With the achievement of single digit mean absolute relative difference (MARD) values (±<10%),[3,16,17] it appears that the necessary accuracy and precision are available to safely adjust insulin doses in basal–bolus insulin regimens.[16] CGM has been approved for adjustment of insulin therapy in Europe but not as yet in the United States.

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Based on information from CGM, insulin infusion can be temporarily suspended, automatically, in response to either *observed* or *predicted* hypoglycemic episodes.[18] Intensive research is underway with development of closed-loop systems involving insulin or dual-hormone (insulin, glucagon) infusion.[19–26]

A voluntary type 1 diabetes (T1D) user community (Nightscout [CGM in the Cloud]) pioneered the development of methods for disseminating real-time CGM data to family and caregivers via the Internet and smartphones.[27] This certainly stimulated and may have accelerated development of commercial systems with similar functionality.[28,29]

A flash glucose monitoring (FGM) system has recently been introduced in Europe that is small, compact, lightweight, and relatively inexpensive, does not require calibration by the user, has a 2-week period of use, and has excellent accuracy.[3,30] This approach provides glucose levels intermittently, when scanned by the user using a receiver or an Android® (Google, Mountain View, CA) smartphone, but currently cannot provide alarms, display rate of change of glucose, or control insulin infusion rates. FGM is presumably intended primarily for patients with type 2 diabetes mellitus.

A panel sponsored by the T1D Exchange recommended that a standardized method, the Ambulatory Glucose Profile (AGP),[31–34] be used to analyze and display retrospective data. This AGP display is currently generated by the FGM system and should be applicable to all CGM systems. However, its use in clinical practice has been limited to date.

Several reviews have summarized the benefits of CGM—alone, in combination with continuous subcutaneous insulin infusion (the ''sensor-augmented pump'') with threshold or predictive low glucose suspension of insulin infusion, and as the critical sensor component of a closed-loop system.[6–26] In contrast to this remarkable, rapid, and very promising evolution of CGM, the real-world clinical acceptance and impact of CGM have been very modest. Observational data of the T1D Exchange show that only a small percentage of patients with T1D are using CGM on an ongoing basis.[35,36] This seems surprising in view of the beneficial effects observed in clinical trials and surveys of users.[30,36,37] Usage by people with type 2 diabetes has been considerably smaller.

Table 1 summarizes some of the salient characteristics of CGM when used in real time by the patient and in a masked ''professional'' mode intended for retrospective review by a healthcare professional. Of course, data collected in the real-time mode can also be analyzed retrospectively by either the patient or the physician.

Table 2 summarizes some of the current CGM systems from Medtronic (Northridge, CA). Two real-time systems from Medtronic can automatically suspend insulin infusion in the presence of *observed* or *predicted* hypoglycemia, respectively. Two additional systems and sensors are intended for professional (masked) use.

Dexcom (San Diego, CA) currently provides two systems: one can be used in either real-time or masked mode (Table 3). One of these has been approved for ''nonadjuvant use'' in Europe, such that it can be used for insulin dosage adjustment, with caveats.

Abbott Diabetes Care (Alameda, CA) provides one system with real-time display (FreeStyle® Navigator® II), one with retrospective display (FreeStyle Libre® Pro), and another (FreeStyle Libre®) with an intermediate type of display

Table 1. Comparison of Real-Time Continuous Glucose Monitoring (CGM) and Masked Professional Analysis of CGM Data

	Real time	*Professional (masked) retrospective analysis*
Intended user	Patient	Physician (HCP), (Patient)
Purpose	Immediate changes in behaviors such as diet, medications, insulin dosage, physical activity; patient education regarding effects of diet, exercise, medications, insulin on glucose levels, variability, and patterns	Estimate quality of glycemic control, magnitude of glycemic variability, times of day with highest risks of hypo- and hyperglycemia Identification of patterns that can be subsequently be used to make long-term changes in diet, medications, insulin, and physical activity, if patterns are stable over days
Patient education	Immediate, continuous	Retrospective, episodic
Representative systems	Medtronic Minimed® 530G, 640G; Dexcom G4®, G5™; Freestyle® Navigator II	Medtronic iPro®2; Dexcom G4®, G5™; FreeStyle® Libre Pro
Real-time display of glucose, rate of change, and graphs	Yes. Immediately available glucose, rate of change of glucose, alerts/alarms, graphical displays. Data from real-time systems can also be analyzed retrospectively.	No. This approach is useful when immediate behavior change is not required or desired (e.g., for some clinical trials).
Comments	One can also perform retrospective analysis of accumulated data.	Exploits signal averaging by combining results from multiple days
	Based on the assumption that glycemic patterns and variability are reasonably stable from day to day. Patterns can be obscured if timing of meals, diet, medication/insulin, or physical activity and exercise vary substantially from day to day.	
Ownership and payment	Patient	Physician, clinic, or institution

HCP, healthcare provider.

Table 2. Selected Characteristics of Selected Continuous Glucose Monitoring Sensor Devices from Medtronic, Inc.

Sensor device	*Accuracy (overall %MARD)*[a]	*Approvals, availability*	*Sensor lifetime*	*Calibration requirement (n/day)*	*Software*	*Smart device compatibility*	*Remote monitoring*
Medtronic Paradigm Minimed® Veo (530G) with Low Glucose Suspend	Enlite sensor: Adults, 13.6 %MARD (FDA filing) 14.2 %MARD (CE mark)	FDA in the United States, CE mark in Europe[c]	Enlite, 6 days	2/day	www.medtronicdiabetes.com/products/carelink-personal-diabetes-software	MiniMed Connect	MiniMed Connect
Medtronic 640G with SmartGuard® (Predictive Low Glucose Suspend)	Enlite sensor: Adults, 14.2 %MARD vs. YSI Children 4–10 and 11–14 years of age for glucose < 121 mg/dL; 21.0 %MARD and 21.5 %MARD, respectively, *vs* blood glucose meters[19,b] Duration of nocturnal hypoglycemia was reduced 50% in 11–14 year olds, 54% in 4–10 year olds.[19,b]	CE mark in 31 countries; Europe and Australia[d]	Enlite, 6 days	2/day	https://www.medtronic-diabetes.com.au/pump-therapy/640g	MiniMed Connect	MiniMed Connect
iPro®2 Professional CGM system		European Union CE mark May 2010; Australia May 2010; South Korea August 2010; Canada March 2011; Japan November 2011; FDA November 2011[e]			www.medtronicdiabetes.com/products/carelink-personal-diabetes-software		
Medtronic iPro®2 with SofSensor sensor	Adults: 9.9% MARD Pediatric patients: 10.1% MARD	Approved by U.S. FDA	6 days	4/day for retrospective calibration; 1 every 12 hours, 3-4 per day recommended	CareLink iPro Therapy Management Software for Diabetes (www.medtronicdiabetes.com/products/carelink-personal-diabetes-software)	Not applicable	Not applicable
Medtronic iPro®2 with Enlite sensor	Adults: 11.0% MARD Pediatric patients: 12.2% MARD	European Union: CE marked May 2010; Australia May 2010; South Korea August 2010; Canada March 2011; Japan November 2011; United States (FDA) November 2011[f]	3 days	Lifetime of 72 h Calibration once every 12 h, 3-4/day recommended	CareLink iPro Therapy Management Software for Diabetes (www.medtronicdiabetes.com/products/carelink-personal-diabetes-software)	Not applicable	Not applicable

[a]Percentage mean absolute relative difference (%MARD) values should be interpreted with caution because few direct comparative studies are available within or between device manufacturers; experimental design and methods of calculation may vary considerably.[2,41,58–60] See also iPro™2 User Guide 2010 Spring 2014 update Mp6025651-022_b; http://www.accessdata.fda.gov/cdrh_docs/pdf12/p120010s046b.pdf, http://www.accessdata.fda.gov/cdrh_docs/pdf12/p120010b.pdf, http://professional.medtronicdiabetes.com/minimed-530-g.

[b]%MARD as recalculated by the present author using data of Buckingham et al.,[19] Supplementary Table 9. Assessment of Sensor Accuracy (http://care.diabetesjournals.org/content/suppl/2015/05/13/dc14-3053.DC1/DC143053SupplementaryData.pdf), pooling data for glucose ranges 71–120 mg/dL and < 70 mg/dL, expressed as median of %MARD for control and intervention nights for all subjects 4–14 years of age.

[c]Algeria, American Virgin Islands, Andorra, Argentina, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belgium, Bolivia, Bosnia-Herzegovina, Brazil, Brunei Darussalam, Bulgaria, Canada, Cayman Islands, Chile, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Faroe Islands, Finland, France, French Guyana, Germany, Greece, Guadeloupe, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Iran, Iraq, Ireland, Israel, Italy, Ivory Coast, Japan, Jordan, Kazakhstan, Kenya, Kuwait, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macedonia, Malaysia, Malta, Martinique, Mexico, Montenegro, Morocco, Namibia, Nepal, The Netherlands, New Caledonia, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Panama, Paraguay, Peru, the Philippines, Poland, Portugal, Puerto Rico, Qatar, Reunion, Romania, Russian Federation, San Marino, Santo Domingo, Saudi Arabia, Serbia, Singapore, Slovenia, South Africa, Spain, Sudan, Sweden, Switzerland, Taiwan, Tanzania, Thailand, Trinidad Tobago, Tunisia, Turkey, Ukraine, the United Kingdom, the United States, Uruguay, United Arab Emirates, Venezuela, and Vietnam.

[d]Western Europe, Central and Eastern Europe, Middle East/Africa, Latin America, Canada, Japan, Australia, Taiwain, India, and Singapore.

[e]Africa, Australia, Austria, Azerbaijan, Bangladesh, Belarus, Belgium, Bosnia, Herzegovina, Brazil, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Germany, Finland, Spain, Europe, France, Greece, Hong Kong, India, Indonesia, Israel, Italy, Japan, Kazakhstan, Latin America, Latvia, Macedonia, Hungary, Malaysia, Montenegro, The Netherlands, New Zealand, Norway, the Philippines, Russia, Poland, Portugal, Puerto Rico, Republic of Korea, Romania, Switzerland, Serbia, Singapore, Slovenia, Slovenska, Sri Lanka, India, Finland, Sweden, Taiwan, Thailand, Turkey, Ukraine, the United Kingdom, the United States.
CE Mark, see (ec.europa.eu).

[f]As in (e), with the exception of the United States.

FDA, Food and Drug Administration.

Table 3. Recent Continuous Glucose Monitoring Sensors from Dexcom Inc. and Animas

Sensor device[a]	*Accuracy (overall %MARD)*[a]	*Approvals, availability*	*Sensor lifetime*	*Calibration requirement (n/day)*	*Software for analysis*	*Smart device compatibility*	*Remote monitoring*
Dexcom G4® PLATINUM CGM[b] (released 2012), approved for adults 18 years of age and older and pediatric patients 2–17 years old	Adults:[b,58–60] 13% MARD Pediatric patients[b]: 15% MARD	Approved by FDA, CE mark; available in the United States as a professional version; available in European Union countries, Middle East, South America, Australia, New Zealand.[c] Also available integrated with the Animas Vibe pump	7 days	2/day	Dexcom Studio (www.dexcom.com/dexcom-studio)	No	Share™
Dexcom G5™ [d] Mobile CGM (released 2015), approved for ages 2 years and older[d]	Adults[d]: 9% MARD Pediatric patients: 10% MARD[d]	U.S. FDA for ''adjuvant use'' only; CE mark from European Union,[e] approved for ''nonadjuvant use''; can eliminate the need for confirmatory fingersticks, for daily glucose management decisions[f]	7 days	2/day	Dexcom Clarity: diabetes management software for Mac and PC (www.dexcom.com/clarity)	Apple iPhone 4S and subsequent iOS models (www.dexcom.com/compatibility)	Remote viewing of glucose levels and trends (www.dexcom.com/faq/what-devices-are-compatible-dexcom-cgm-apps)

[a]Mean absolute relative difference (%MARD) values should be interpreted with caution. Only a few direct comparative studies are available between device manufacturers.[2,58–60] See also Joubert et al.[41]

[b]Adults, Software (505): http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S018b.pdf, Pediatrics, Software (505): http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S031b.pdf, Dexcom G4 PLATINUM CGM User Guide, 2012; RPT-902345, Report of Effectiveness and Safety of the Dexcom G4 PLATINUM with Spritz Algorithm Continuous Glucose Monitoring System: http://www.dexcom.com/en-GB; RPT-902628, Effectiveness and Safety Study of the Dexcom G4 PLATINUM with Spritz Algorithm Continuous Glucose Monitoring System in Pediatric Subjects with Diabetes Mellitus: http://www.dexcom.com/en-GB.

[c]Sweden, Finland, Germany, Austria, Switzerland, Italy, Benelux, Czech Republic, Slovak Republic, the United Kingdom, Ireland, Spain, Portugal, Norway, Australia, New Zealand, France, Poland, India, Israel, Slovenia, United Arab Emirates, Kingdom of Saudi Arabia, South Africa, Denmark, Chile, Turkey, Hong Kong, and Hungary.

[d]Dexcom G5 Mobile User Guide 2015.

[e]Sweden, Finland, Germany, Austria, Switzerland, Italy, Benelux, Czech Republic, Slovak Republic, the United Kingdom, Ireland, Spain, Portugal, Norway, France, Poland, Denmark, and Hungary.

[f]Caveat regrading insulin dosage adjustment: ''If … glucose alerts and readings do not match … symptoms or expectations, … should obtain a [capillary blood glucose measurement]'' (www.dexcom.com/en-GB).

Table 4. Selected Characteristics of Flash Glucose Monitoring and Continuous Glucose Monitoring Sensor Devices from Abbott Diabetes Care

Sensor device	*Accuracy (MARD)*[a]	*Approvals, availability*	*Sensor lifetime*	*Calibration (n/day)*	*Software*	*Smart device compatibility*	*Remote monitoring*
FreeStyle® Libre Flash glucose monitoring system	11.4% MARD[3] 10.0% MARD *vs* Blood Glucose Meter; 10.7% MARD *vs* YSI[b]	CE mark; for ages ≥18 years of age in the United Kingdom, France, Germany, Spain, Italy, The Netherlands, Sweden, and Austria	14 days	No calibration required by end-user	FreeStyle Libre software (https://abbott-diabetes-care.at/software.html)	LibreLink (approved third-party software for Android)	Summary reports (pdf format) to HCP or caregiver via e-mail
FreeStyle® Libre Pro Flash glucose monitoring system	11.1% MARD	CE mark; for ≥18 years of age in India	14 days	No calibration required by end-user	FreeStyle Libre Pro software (https://abbott-diabetes-care.at/software.html)	Not available	Not available
FreeStyle® Navigator II CGM system	12.3% MARD	CE mark; for ≥6 years of age[c] in Germany, Denmark, Norway, The Netherlands, the United Kingdom, Sweden, Israel, and France	Up to 5 days	4 calibrations on Day 1; 1 calibration on Day 3	FreeStyle Navigator Plug-in software (https://abbottdiabetescare.co.uk/our-products/other-meters/freestyle-navigator-2)	Not available	Not available

[a]Mean absolute relative difference (MARD) values should be interpreted with caution because few direct comparative studies are available within or between device manufacturers[2]; experimental design and methods of calculation vary considerably. See also Joubert et al.[41]

[b]Ji L, Guo X, Guo L. Presented at the Chinese Diabetes Association, 2015, and at a symposium associated with the World Congress of Diabetes (International Diabetes Federation) Vancouver BC, December 2015. (L.K. Lyons, personal communication.)

[c]Supervision by a caregiver ≥18 years of age is required for individuals 6–17 years of age.

designated as FGM (Table 4). For purposes of the present review, FGM is regarded as a subset of the more general, inclusive term, CGM.

Barriers to Clinical Implementation

If CGM systems can perform so well, why haven't they been more widely used?

There have been many discussions regarding the barriers (discussed below) to implementation of technology in the clinical management of diabetes.[10,11,36,37]

We shall discuss some of these barriers here.

The physician and clinical inertia

The physician is often cited as being one of the major barriers to implementation of *insulin therapy*. Introduction of any new modality of therapy requires time, energy, effort, judgment, and initiative. When this is coupled with demands on physician time that are impossible to meet during extremely brief clinical visits, lack of reasonable reimbursement for physician time, lack of reimbursement for ancillary resources required to support CGM (e.g., office staff, computers, printers, Internet access, and information technology support services), potential medical–legal liability, and the uncertainties associated with any new intervention, there should be no surprise that there has been clinical inertia for CGM implementation in clinical care. Very few physicians have developed or adopted a systematic approach to interpretation of CGM data, and there are no training courses. Physicians generally do not have the time to familiarize themselves with methods serving a minority of patients. Accordingly, CGM has literally been left primarily in the hands of the patient. Representatives of device manufacturers provide limited support. There is need for considerable education regarding use of CGM for the physician and the entire ''healthcare provider'' community—including specialists in endocrinology and diabetes, primary care providers, other medical specialists, nurse practitioners, physician assistants, and certified diabetes educators. There is an urgent need for fully automated and standardized interpretation of glucose data and patterns, akin to automated electrocardiogram interpretation, designed for both physicians and patients.

Two additional factors come into play in the education of physicians. Representatives of pharmaceutical companies have traditionally played an important role in physician education. That has been less often the case for medical device companies. Medical specialty organizations provide clinical practice guidelines and recommendations, medical/scientific journal publications, and postgraduate training courses.[11,38–41] These avenues will need to be expanded with regard to CGM.

Usability and the human interface

Today there is clear recognition of the critical role of usability and the human interface. Numerous studies have been performed to optimize many other types of medical devices.[42] Diabetes-Mine has called attention to this area with competitive awards for advances in usability.[43]

Device manufacturers have made many improvements in usability. However, there are few published studies addressing usability and human interface issues for CGM devices and sensors. There is a need for some old-fashioned time-and-motion studies:

1. How much time and training are required for the clinician to learn and then teach the patient the basics of operation and a systematic approach to use CGM data?
2. How much time and training are required by the patient to become familiar with the use of the device, insertion and removal of the sensor, routine daily use, and transmission of the data to a computer and the Internet?
3. How much time and training are required for the physician and/or patient (individually or jointly) to perform and interpret retrospective data analysis?
4. How reliably, consistently, and effectively do physicians and patients interpret and apply the results?
5. How well does information obtained from CGM get translated into actions and behaviors that improve measurable clinical outcomes, including quality of glycemic control and glycemic variability, treatment satisfaction, and quality of life?

Automated data transfer of glucose data to the Internet has been revolutionary.[27–29] Ease of use of devices and data by the patient and family or other personal caregivers represents another usability issue. It remains to be seen the extent to which an implantable sensor (e.g., one under development by Senseonics[44]) will alleviate or introduce different human factors issues. The original implantable sensor developed by Dexcom was not been pursued commercially to date.[45]

Accuracy and precision

Until recently, the accuracy and precision of CGM had been so far inferior to those of blood glucose meters for measurement of capillary blood glucose such that there was increased risk of error in the clinical application of CGM values. Accuracy and precision have improved dramatically.[2–5,16,17,41,46] For a wide range of glucose values, CGM data are accurate enough to use for self-adjustment of insulin dosage, detection of hypoglycemia, and evaluating response to therapy. Accuracy is strongly dependent on the glucose level[47] and rate of change of glucose.[4] Accuracy in the hypoglycemic range is still limited, but hopefully this will continue to improve.

Regulatory approval for use for adjustment of insulin therapy

In the United States, lack of approval for use of CGM data for adjusting insulin in ambulatory, hospital, and intensive care unit settings is an impediment to more widespread adoption. This lack of approval is likely to have had a negative impact on reimbursement. Accuracy of CGM today is better than the accuracy of blood glucose meters when they first became available 35 years ago, when they were already being used for self-adjustment of insulin dosage. The additional information from graphical displays, rate of change, and alarms can enhance the effectiveness of CGM devices.[16,17]

Cost

Cost is a major factor. Health plans, insurance companies, and governments in most countries throughout the world do not cover CGM. Medicare has approved reimbursement only selectively for retrospective, but not real-time, CGM for people with T1D in the United States. One also needs to consider costs to society *for failure to implement CGM*, including costs of emergency management of severe hypoglycemic episodes

(emergency room visits, hospitalizations, mortality, and morbidity), the costs of failure to achieve the optimal level of glycemic control in terms of quality of life, and long-term complications. It is difficult to evaluate costs to the individual because of diversity of pricing systems.

Sensor lifetime

Sensor lifetime is another factor that contributes to cost, inconvenience, and slow user acceptance. Even the durability of the adhesive used for attachment of the sensor to the skin is a matter of concern. One can expect that user acceptance will continue to improve as sensor lifetime increases and ease of sensor insertion improves.[3]

Calibration

Calibration using capillary blood glucose meters and reagent strips involves cost, discomfort, and inconvenience, increases the number of devices and complexity, and may add psychological burden. This issue has been completely resolved in the case of Abbott's FreeStyle Libre,[3] which is precalibrated in the factory and requires no further calibration by the user (not currently approved by the Food and Drug Administration in the United States). Hopefully, similar kinds of technical advances can be incorporated into other CGM devices as well.

Commitment to intensive insulin therapy

Use of CGM with or without an insulin pump usually represents a commitment to long-term intensive insulin therapy, which includes the patient–physician relationship, several costs, human factors, and psychological issues.

User experience

The user must be educated so that he or she understands the potential benefits and potential issues related to use of CGM. This includes the initial training regarding mechanics of insertion and removal of the sensor, use of a transmitter, receiver, ancillary devices (smartphones, the Internet, a computer, software), and contingency planning in the event of device malfunction. Patients need to be trained so that they become confident in their ability to translate information derived from the CGM device into appropriate actions. They should be followed after the training to verify that they can benefit from the technology. Characteristics of successful users of CGM have been studied using survey methodology.[48] Frequent use of CGM and use of a cautious conservative approach to corrections in response to CGM data (thereby avoiding overcorrections) were identified as key features of success.

Inconvenience

Any intervention can have unintended consequences. False alarms for hyper- and hypoglycemia are annoying. Gaps due to transmission failures from sensor to receiver had previously been a significant problem[49] but now are mostly resolved. Erroneously low glucose readings and false alarms due to physical compression of tissue around the sensor have been ongoing problems.[50] In principle, the latter could be resolved by use of redundant sensors in two or more locations on the body, but this would impose burden and cost.

Potential rapid obsolescence

CGM technology performance and functionality are evolving so rapidly that any device obtained today is likely to be superseded in the near future. This contributes to the financial barrier. Of course, one can continue to use devices of older vintage.

Controversy regarding clinical benefits

There will always be some variation in results among studies due to a myriad of factors ranging from the patient population to subtleties of experimental design and protocols, and variability in the implementation of the protocol. The Hawthorne effect, choice of end points, and random statistical fluctuations contribute to the heterogeneity of results. One cannot expect perfect concordance. In many types of studies that involve dosage titration of pharmaceutical agents (treat to target, and variations thereof), one does not expect any differences in HbA1c. Rather, one needs to consider HbA1c and the risk of hypoglycemia simultaneously.[51–53] When evaluating a CGM technology, the question should not be, ''Did the use of CGM result in a change in HbA1c?,'' nor should it be, ''Did the use of CGM result in a favorable change in the risk of hypoglycemia?'' Instead, the question should be, ''Did the introduction of CGM result in a change in the relationship between risk of hypoglycemia and HbA1c achieved?''[51–53]

Delays and associated biases in meta-analyses and reviews to evaluate clinical impact

Studies evaluating clinical and cost-effectiveness are typically published a few years after a device or technology has been introduced. The technology may have changed so much (e.g., perhaps with improvement in accuracy or usability) that the cost-effectiveness study may be obsolete by the time the data are published.[54] This is likely to be one of the reasons for failure of reviews based on meta-analysis to identify the effectiveness of CGM.

Instability of patterns and reproducibility to results

Patient responses to the current glucose level, to arrows indicating rate of change of glucose, and qualitative analysis of a graphical display of glucose versus time do not require stability of patterns. Similarly, use of CGM for a closed-loop system does not require day-to-day stability of glucose patterns. However, if patterns are stable from day to day, the control algorithm for the closed-loop system may be able to exploit that additional information. In contrast, retrospective analysis of either real-time or masked CGM is dependent on stability of patterns from day to day. Use of the AGP and of related forms of analysis implicitly requires stability and reproducibility of glucose patterns from day to day.[31–34] If glucose patterns are erratic, one may not be able to conclude anything other than the fact that the patterns are erratic. By widening the size of the time window used for retrospective analysis to 1, 2, or 4 weeks to construct an AGP, one is able to take advantage of signal averaging: random noise will tend to cancel out, revealing the underlying pattern. If the time window of observations becomes too large, then day-to-day instability and heterogeneity will blur the pattern and degrade the quality of the information obtained. Ideally, the CGM

data should be interpreted together with additional accurate, objective information regarding diet, physical activity, medications (including insulin), and other factors.

Lag time of interstitial fluid glucose relative to blood glucose

There is a delay as glucose is transported from blood to interstitial fluid. This delay could be appreciable in early forms of CGM (e.g., 15 min). Largely because of improvements in algorithms for computing glucose from the raw electrical signal from the sensor, this problem has been dramatically reduced to only a few minutes for several systems.

Confusion regarding reporting of accuracy and precision of CGM sensors

Numerous methods have been proposed for measurement of accuracy and precision of CGM and SMBG. The precision and accuracy, usually measured by %MARD, can vary dramatically in a smooth relationship with glucose level.[47] Results should be reported in this manner. Furthermore, results vary systematically with rate of change of glucose with time.[4] Accordingly, one should report %MARD as a smooth function of both glucose level and rate of change, using either a family of curves or a three-dimensional surface. When evaluating performance of sensors designed to suspend insulin infusion in response to actual or predicted hypoglycemia, one should focus on the %MARD for the glucose levels of greatest interest (e.g., 71–120 mg/dL and <70 mg/dL). The %MARD depends on whether the reference measurements are obtained using a blood glucose meter or using a more accurate and precise device such as a Yellow Springs Instrument glucose analyzer with ±2% accuracy. The *% median* absolute relative difference, sometimes designated %Med(ARD), is, on average, 0.8 × %MARD. This has been demonstrated empirically by analysis of data from multiple studies and is supported by numerical simulations and based on statistical theory (author's unpublished observations). In turn, %MARD is approximately 0.8 × %CV, where %CV is the coefficient of variation of replicated measurements.

Confusion regarding interpretation of glycemic variability

More than two dozen metrics have been proposed for glycemic variability.[55] There are multiple forms of variability: overall, within days, within short time segments, nocturnal, between days, between daily means, (between hourly means or medians by time of day in the average circadian pattern), postprandial excursions, and instability of patterns from day to day or by day of the week. Each of these characteristics can be measured objectively. Nearly every measure of glycemic variability is very highly correlated with the overall or total SD (SD_T) calculated using all glucose values from all days, so SD_T remains the gold standard.[55,56] It is often desirable to express the SD_T as a coefficient of variation or $\%CV_T$, where $\%CV_T = 100 \times SD_T/\text{Mean}$,[56] and to interpret variability ($\%CV_T$) relative to an appropriate identified reference population using either percentiles[56] or *z*-scores.[57]

Discussion

CGM and FGM device manufacturers are addressing the several barriers discussed above. We are approaching a tipping point, a watershed, where the accuracy of several CGM sensors has improved to the point where *nonadjuvant use* for insulin dose adjustment can and will be approved by all countries as safe and effective. This will improve availability—rapidly and dramatically leading to widespread acceptance, and better coverage from health plans, insurance companies, and governments.

Integration of CGM with insulin infusion pumps includes both threshold and predictive low glucose suspend (available now), as well as hybrid- and fully automated closed-loop systems using either insulin alone or insulin and glucagon, currently in or approaching pivotal trials.

Patients and their physicians should welcome the tremendous progress of CGM technology to date. As advances in technology and clinical evaluation continue, one hopes and expects that increased popularity will generate economies of scale, drive further cost reductions, and further improvement of usability, sparking the interest of patients and healthcare providers, and further stimulating usage.

Conclusions

CGM has shown impressive scientific, technological, engineering, and clinical advances, providing benefits to many people with diabetes. Several barriers to use of CGM persist, but these barriers are being addressed. Utilization of CGM can be expected to increase, improving both patient outcomes and public health. The physician is at once a key enabler and an important barrier. Education of physicians and patients is key. Advances in accuracy, additional approvals for use of CGM for adjustment of insulin dosing, and automated interpretation of results should spur wider usage and acceptance.

Acknowledgments

The author thanks Helena W. Rodbard, MD and Matthew Maryniak for review of the manuscript.

Author Disclosure Statement

The author previously served as a consultant to several manufacturers of blood glucose meters and CGM devices. Dr. Rodbard is a consultant to One Drop. No competing financial interests exist.

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