

In Brief

Continuous glucose monitoring (CGM) technology has the potential to revolutionize diabetes care in the near future because of the real-time feedback it provides about therapeutic interventions and variations in lifestyle or dietary intake. In short, CGM has made the attainment of near-normal blood glucose concentrations an achievable goal for most patients with diabetes. Several challenges remain to be addressed, however, including the high cost of the devices, limitations in approved clinical uses, and insurance coverage for the technology. This article reviews the CGM technology currently available in the United States, its approved uses, and its limitations.

Continuous Glucose Monitoring: The Future of Diabetes Management

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There is a long history of technological advances being translated into improved diabetes management. A few examples include the discovery and mass production of insulin, the adoption of simple urine testing for glucose and ketones, the development of effective oral diabetes medications, the development of accurate capillary blood glucose measurement devices, and the refinement of practical and reliable subcutaneous insulin infusion pumps. More recently, engineering and scientific advances have allowed the development of continuous glucose monitoring (CGM) devices that have proven useful for the day-to-day management of diabetes. Although these devices are expensive and not yet widely adopted by diabetes practitioners or patients, they have the potential to revolutionize diabetes care and make the attainment of near-normal blood glucose concentrations a reality.

CGM: A Significant Advance in Diabetes Care

Accurate determination of blood glucose concentrations is a prerequisite for the application of state-of-the-art intensified diabetes management. Until very recently, this determination could only be achieved by the attainment of multiple capillary blood glucose determinations each day, a practice that is cumbersome, inconvenient, expensive, and a significant disincentive to achieving target blood glucose goals. Even when applied conscientiously, self-monitoring of

blood glucose (SMBG) provides only a snapshot blood glucose concentration without providing any information about the direction or rate of blood glucose change. As a result, many patients are unable to achieve blood glucose targets despite testing their blood glucose multiple times daily. CGM represents a significant advance because it 1) provides real-time information about current blood glucose (or, more accurately, interstitial fluid glucose) concentrations, 2) provides short-term feedback about the effectiveness of diabetes interventions (such as insulin administration), and 3) it provides warnings when blood glucose concentrations become dangerously high or low.

The purpose of this article is to provide a review of the strengths and weaknesses of current CGM technology and to provide information about how these devices can best be used in clinical practice for the care of people with diabetes.

Purpose and Target Population

The importance of CGM is best illustrated by an example that many patients with type 1 diabetes face on a daily basis. Suppose that John Doe, who has type 1 diabetes, commutes 60 minutes to work from his home in the suburbs. As recommended by his physician, he consistently checks his blood glucose level immediately before getting into his car and heading home from work at 5:00 p.m. This evening, his blood glucose concentration is 120 mg/dl, whereas just before

lunch it was 90 mg/dl. He consumed his usual lunch of 800 calories, including 100 g of carbohydrate, and he took 12 units of lispro insulin via an insulin pump as recommended by his physician. The question is: Is it safe for John Doe to drive home, or should he eat a snack? He is hesitant to eat a snack because he fears that he will become hyperglycemic before supper, and he is trying to keep his hemoglobin A_{1c} (A1C) < 7%.

There is no correct answer to John Doe's dilemma with the limited information available to him. However, if provided with additional glucose readings that are available with CGM technology, an answer to his dilemma is readily apparent (Figure 1). Despite the fact that his current blood glucose is 120 mg/dl, his CGM sensor, which provides a reading every 5 minutes, clearly demonstrates that his blood glucose concentration is rapidly declining and will most likely be in the hypoglycemic range before he arrives home. Therefore, he should eat a carbohydrate snack before driving home to prevent a motor vehicle accident.

It is reasonable to ask what could account for John Doe's rapid decline in blood glucose after a normal lunch and insulin dose. There are several answers to this question that occur commonly in patients with type 1 diabetes. First, the absorption of his lispro might have been delayed by its injection into a relatively avascular

place in the skin. As has been well documented by many previous studies, the absorption of insulin is altered by the location, skin temperature, and depth of the insulin injection. Second, the rate of gastric food emptying is subject to many variables, including an increased rate during hypoglycemia and a delayed rate during hyperglycemia. If John Doe has subclinical gastric neuropathy, then his gastric emptying may be increased or delayed without his recognition. Finally, his rate of gastric emptying may be altered by his activity, his degree of stress, or the composition of the food that he eats. Therefore, it is not surprising that unpredictable blood glucose values are common in type 1 diabetic individuals.

Who will benefit from CGM?

Two types of diabetic individuals will potentially benefit from CGM. First, as in the example above, all type 1 diabetic patients are candidates for CGM, because all type 1 diabetic individuals are prone to hypoglycemia. These individuals are not able to secrete endogenous insulin and therefore cannot suppress the circulating concentration of insulin when their glucose level is dropping to hypoglycemic levels. Second, type 2 diabetic individuals who are dependent on exogenous insulin (which usually occurs after several years of diabetes) may also benefit from CGM. This is particularly true if they

experience hypoglycemia when trying to maintain their A1C < 7%. In fact, any individual who experiences hypoglycemia will benefit from the hypoglycemia warning that CGM provides.

The above paragraph needs to be tempered with the realization that CGM is not free of problems. First, CGM requires some dexterity with the hands; some patients may have difficulty inserting the sensor because of peripheral neuropathy affecting their hands. Second, CGM requires a minimal level of mechanical ability because of the need to interact frequently with the sensor's readout and to appropriately respond to its alarms. It is not necessary for an individual to use an insulin pump to benefit from CGM, but it is necessary for the individual to use some form of intensive insulin therapy because of the need to check the sensor's readings against finger-stick blood-glucose measurements twice daily. Finally, and most important to CGM users, is the cost of CGM to individuals. Most insurance companies do not routinely cover the cost of CGM, which typically averages \$5–10 per day, depending on the longevity of the glucose sensor. This cost is prohibitive to many individuals.

Review of CGM Technology

CGM systems operate by measuring the glucose levels in interstitial fluid. The devices consist of three components: a disposable sensor that measures glucose levels, a transmitter that is attached to the sensor, and a receiver that displays and stores glucose information. The information stored in the receiver is then converted into estimated mean values of glucose standardized to capillary blood glucose levels measured during calibration.

Using an applicator or self-insertion device, a thin plastic sensor is inserted just under the skin of the abdomen or the upper arm. These devices can display real-time glucose values and glucose trends, and some can also sound an alarm or vibrate when they detect hyperglycemia or hypoglycemia. The receiver can store information for later use, and long-term data can be downloaded to a computer.

Currently available CGM devices are considered minimally invasive enzyme-coated electrodes to measure

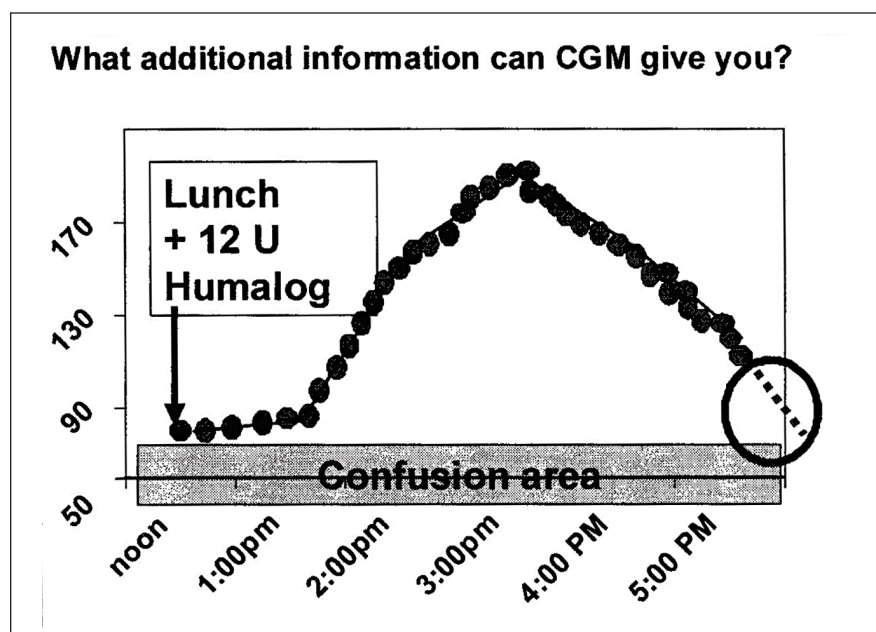


Figure 1. A hypothetical clinical dilemma that can be resolved with CGM technology.

Table 1. A Summary of the Devices Reviewed³

Product	Year Approved	Sensor Type	Sensor Mechanism	Sensor Location	Calibrations per Lifetime of Sensor	Sensor Life Span (hours)	Frequency of Testing (minutes)	Glucose Data Display	Alarm
MiniMed CGMS Guardian	2004	Minimally invasive	Enzyme-tipped catheter	Subcutaneous arm	12	72	5	Real-time	Yes
DexCom STS	2007			Subcutaneous abdomen	2	168	5		Yes
Abbott Freestyle Navigator	Under FDA review			Subcutaneous arm	1	72	1		Yes

interstitial glucose concentrations and convert these values to blood glucose levels. The catheter has electrodes impregnated with glucose oxidase, which is introduced into the subcutaneous tissue. The reaction between interstitial fluid glucose and glucose oxidase located on the electrode produces hydrogen peroxide. This reaction converts the interstitial glucose into an electrical current proportional to the glucose concentration at the site of the catheter insertion. Devices using enzyme-coated catheters require frequent calibrations to correct variations in the reaction between the electrode and the subcutaneous tissue, as well as fluctuations in glucose and oxygen diffusion at the site of the electrode.^{1,2}

There are currently three CGM systems available in the United States. These devices are reviewed below and summarized in Table 1.

Medtronic MiniMed Guardian

This device, approved by the U.S. Food and Drug Administration (FDA) in 2006, has several advantages over the previously available MiniMed Gold, a primitive device that did not display real-time glucose results and required downloading of data to a computer every 72 hours for visualization. The Guardian reports glucose values in real-time, allowing patients to respond immediately to glucose excursions. In addition, it reports the trend of the glucose values in numerical and graphic depictions. Glucose values are sent wirelessly to the monitor at a range of up to 6 feet. The Guardian also has an alarm system to detect hyperglycemia and hypoglycemia.

DexCom Short-Term System (STS)

The DexCom STS is available with a 7-day sensor that was approved for use in 2007. It uses a glucose oxidase-coated catheter inserted subcutaneously into the abdomen. The glucose concentration is measured every 5 minutes, and values are transmitted in real-time to an adjustable wireless receiver. The STS has a built-in alarm system to alert patients to glucose excursions. It requires two calibrations daily during the life span of the sensor.

Abbott Diabetes Care Freestyle Navigator

The Navigator is a minimally invasive CGM device that received FDA approval just as this issue was going to press. It also uses a glucose oxidase enzyme-coated catheter inserted subcutaneously. Glucose readings are performed every minute for up to 72 hours and are presented as real-time data. The transmitter sends data wirelessly to a receiver up to 10 feet away. The Navigator provides the trend of glucose values as indicated by an arrow visible on the monitor. The arrow indicates whether the glucose value is stable (horizontal), increasing (arrow up), rapidly increasing (arrow sharply up), decreasing (arrow down) or rapidly decreasing (arrow sharply down). Glucose values can be downloaded to a computer for retrospective review. The device has an alarm system to indicate glucose excursions outside a preset range. Compared to other enzyme-based catheter systems, the Navigator only requires one calibration during a 72-hour period.^{1,3}

Other CGM systems

The MiniMed Paradigm REAL-Time System integrates the Paradigm 522 or 722 continuous subcutaneous insulin infusion pump with a CGM system. Patients wear a sensor and transmitter for up to 3 days at a time. The measured interstitial glucose levels are sent wirelessly to the insulin pump monitor, which displays a 5-minute glucose average. In addition, The FDA approved the Medtronic iPro Recorder in January 2008. This product will be available for physician-only use and not for patient purchase. Patients borrow the iPro Recorder from their physician and wear it for 3 days. The iPro is similar to the sensor-transmitter device used in the Paradigm pump described previously and records 72 hours of glucose data on a tiny chip. A monitor is not provided for patients to view glucose values at home. Instead, the device is downloaded at the physician's office after the recording period has been completed.

Accuracy and Comparison With Capillary Blood Glucose

Are CGM devices accurate enough to replace finger-stick measurements?

CGM systems have the potential to greatly affect the management of diabetes. Before they gain widespread acceptance, however, physicians and patients will need to feel confident about the ability of these devices to provide an accurate reading of blood glucose. The accuracy of the currently available devices has been studied by a number of investigators, and many report limited sensitivity, particularly in the detection of hypoglycemia. A

variety of methods have been used to evaluate the accuracy of the devices, including relative absolute difference and error grid analysis. Relative absolute difference is calculated by subtracting the reference glucose from that obtained by the device, then dividing this by the reference value and multiplying by 100 to obtain a percentage. The lower the percentage is, the greater the accuracy of the device.

The Diabetes Research in Children Network (DirecNet) is a network of five clinical centers whose focus is the use of glucose monitoring technology in children with type 1 diabetes. It has evaluated the accuracy of the Medtronic first- and second-generation CGM systems. Using the relative absolute difference, these and other studies have found that first- and second-generation CGM devices (not reviewed here) routinely over-reported nocturnal hypoglycemia with a high false detection rate.

Bode et al. compared home blood glucose monitors with the results obtained using Medtronic's MiniMed Guardian and found an absolute relative error of 21.3%, with the sensor reading an average of 12.8 mg/dl lower than the conventional home meter.⁴ In this study, the effect of real-time alarms on glucose excursions was also evaluated, with the hyperglycemia alarm able to detect values ≥ 250 mg/dl with a sensitivity of 63%, specificity of 97%, and false alarm rate of 19%. Hypoglycemia alarms detected values of ≤ 70 mg/dl with a sensitivity of 67%, specificity of 90%, and false alarm rate of 47%. Although the sensitivity and specificity are poor, the investigators found that alarms significantly reduced the duration of hypoglycemic excursions.

Garg et al. evaluated DexCom's CGM 7-day sensor and found a mean relative absolute difference of $13 \pm 10\%$ when measured in the hypoglycemic (< 70 mg/dl) range, $20 \pm 22\%$ in the euglycemic range, and $33 \pm 32\%$ in the hyperglycemic (> 180 mg/dl) range.⁵ With the low alert set at 80 mg/dl, hypoglycemia was detected with 88% sensitivity, 91% specificity, and 54% positive predictive value. Using fixed-point Clarke error grid analysis, the investigators found that 97% of values fell in the clinically acceptable zones A and B, as described below.

Some have suggested that the reduced accuracy in the hypoglycemic range, especially at night, may be the result of the lack of constant lag period between interstitial and plasma glucose. If true, this would have implications about the best time to calibrate the monitor. Techniques such as those proposed by Feldman et al., where calibration only occurs during periods of slow glucose change, may help to improve accuracy and reduce the occurrence of false alarms.⁶

DirecNet, using the CGMS Gold, compared calibration techniques and found that increasing the number of calibrations had only a modest effect on accuracy, but that calibrating during times of glucose stability and placing less emphasis on daytime calibration for nighttime values may have a greater impact on accuracy.⁷

Clearly, evaluating the accuracy of these devices is not simple because most conventional measures of accuracy, such as correlation, regression, or even the original Clarke error grid, compare measurements taken during static points in time and fail to take into account the temporal nature of the values. The continuous glucose error grid appears to be a more appropriate measure of accuracy, but it is time-consuming, and some are concerned that this method may fail to detect differences in accuracy between devices.

Although the currently available data suggest limited accuracy of these devices compared to capillary blood glucose measurement (especially in the hypoglycemic range) and point to the need for improvement in the technology, it is important to remember that both CGM and capillary measurement have limitations and that both provide estimates of plasma glucose concentration as determined by a gold standard assessment. Nobody knows for certain which method provides the better estimate for the purposes of diabetes management, and some have even argued that the brain is bathed in a fluid that resembles interstitial fluid more closely than blood. Moreover, it is also important to remember that capillary blood glucose measurement has limited accuracy in assessing glucose concentrations in the hypoglycemic range. In the end, we must assess whether CGM provides information that is accurate enough

to be clinically useful and to improve diabetes care. Finally, it is important to remember that CGM is best used as an adjunct to capillary monitoring and not a replacement for it.

Clinical Indications and CGM

Initiation

The FDA lists the following indications for CGM: detecting trends and tracking patterns of glucose values; serving as an adjunct to, but not a replacement for, information obtained from standard home blood glucose monitoring; aiding in the detection of episodes of hyperglycemia and hypoglycemia and minimizing glucose excursions; and facilitating acute and long-term therapy adjustments. All devices are indicated for patients ≥ 18 years of age, but only the MiniMed Guardian and Paradigm REAL-Time systems are approved for use in children age 7–17 years. The FDA advises that the use of CGM is not intended to replace home blood glucose monitoring and that it should only be used in conjunction with patient self-monitoring. Further, treatment decisions based on CGM results should be confirmed by a traditional blood glucose meter.

Hypoglycemia

According to several authors, nocturnal hypoglycemia may account for nearly two-thirds of the justification for prescribing CGM to diabetic patients.⁸ Nocturnal hypoglycemia is often asymptomatic, even in those with normal glucose awareness while awake.⁹ This can be particularly important in children, in whom the literature suggests 30% of CGM recordings revealed nocturnal hypoglycemia < 40 mg/dl.⁸

Hyperglycemia

In many diabetic patients, daytime hyperglycemia may be easily overlooked. This may either be a result of insufficient adherence to blood glucose self-monitoring or monitoring practices that do not cover the entire day. CGM can be particularly useful in detecting postprandial hyperglycemia. Diabetic patients are typically trained to monitor blood glucose before meals and at bedtime, but rarely several hours after a meal. CGM may also help detect nocturnal hyperglycemia and those with the dawn phenomenon or somogyi effect. The dawn phenomenon describes

Three Day Record in a Type 1 Diabetic Person with Hypoglycemic Unawareness

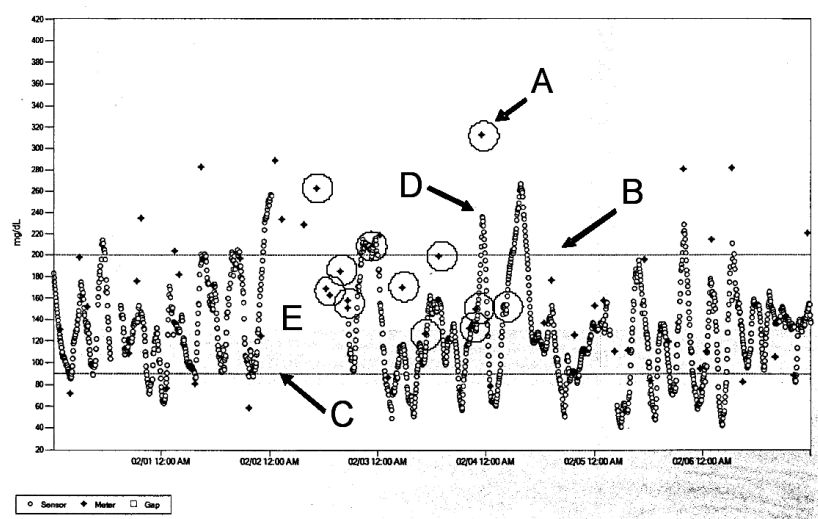


Figure 2. Components of a CGM record over a 3.5-day period: (A) The circled time points indicate the capillary blood glucose measurements that are done not only to standardize the CGM system but also to double-check the CGM-reported readings. Some of the capillary blood glucose readings have been circled. Notice that when there is a rapid change in glucose concentration, the CGM's glucose concentration does not equilibrate with the finger-stick glucose. (B) This arrow indicates the upper limit of the high glucose alarm, which is set by patients. This alarm permits patients to take additional insulin for unexpected hyperglycemia. (C) This arrow indicates the lower glucose alarm, which is also set by patients. Setting the alarm too high will result in multiple alarms; therefore, patients must decide at what level they would prefer to be alerted when their glucose is dropping. This alarm is usually set between 70 and 90 mg/dL. (D) This arrow points to the frequent readings from the CGM system. In this case, the reading is provided to the patient every 5 minutes in graphical form. (E) In this area of the monitoring graph, there was no communication between the CGM sensor and the CGM receiver. The most common reason for this occurrence is that the sensor stopped working and a new sensor needed to be inserted.

early morning hyperglycemia as a result of growth hormone release in early morning hours, whereas the somogyi effect describes fasting hyperglycemia as a result of the counter-regulatory hormone response to hypoglycemia in the middle of the night.¹⁰

Guiding adjustments in treatment

CGM can provide more detailed information regarding blood glucose fluctuations than self-monitoring alone. This is of particular importance in patients with labile glucose values who experience hypoglycemia in response to intensification of insulin therapy. CGM can track the glucose response to changes in insulin therapy and can help patients and physicians determine whether the insulin adjustments were correct. In addition, patients have more glucose data available to guide them in adjusting their insulin dosing ratios

at mealtime, as well as adjusting therapy based on glucose fluctuations related to exercise, illness, or new medications.³ CGM use may also be advantageous in vulnerable populations or situations, such as pediatric patients, gestational diabetic patients, and critical care patients.¹⁰

Patient education

Readings stored in a CGM system can be downloaded to a personal computer and printed out for retrospective review (Figure 2). The tracings can provide a graphical depiction of the fluctuations in blood glucose levels, which may be easier to comprehend for some patients compared to a traditional logbook. As a result, patients may be afforded a better understanding of the therapeutic duration of prandial insulin, the impact of insulin pump malfunction (such as when a pump catheter is obstructed) on glycemic excursions, and the effect of

meals, exercise, and lifestyle modification on glucose values.⁸

Getting patients started

There are numerous strategies available by which patients can become educated about CGM systems and use them successfully. The most effective method is to provide a comprehensive and multidisciplinary approach involving patients, physicians, certified diabetes nurse educators, and even the local sales representative for the particular brand of CGM prescribed. Interested patients can be initially screened by their physician for confirmation that they meet indications for CGM monitoring. This evaluation should elucidate precisely how CGM might facilitate improvement in diabetes management.

Once the indication for CGM use is identified, patients should be referred to a qualified diabetes professional to be taught how to use the device, insert the catheter, obtain glucose readings, download stored information to their home computer, and perform any maintenance required to keep the device functional. The goal is for patients to leave this visit feeling comfortable using the prescribed device and to be able to accurately obtain and apply data from the monitor to improve glucose control. In many cases, this visit may be coordinated with the manufacturer's representative to provide detailed knowledge of the particular CGM device and information about how to obtain supplies in a timely manner. Patients should also be given a reference booklet that they can refer to, such as the excellent *CGM Guide* by Edelman and Bailey.¹¹ This guide offers patient-directed education and case-based scenarios to help patients use the CGM system effectively and troubleshoot problems. A list of Internet resources offering additional information about CGM systems is provided in Table 2.

Figure 2 shows a typical CGM data readout after data are downloaded to a computer. Patients should be familiar with each of the highlighted events that are depicted and should be instructed on how to react to each event. Refer to the figure legend for explanation of each of the highlighted events.

After using the device for ~ 1 week, patients should return to their diabetes provider to review the data

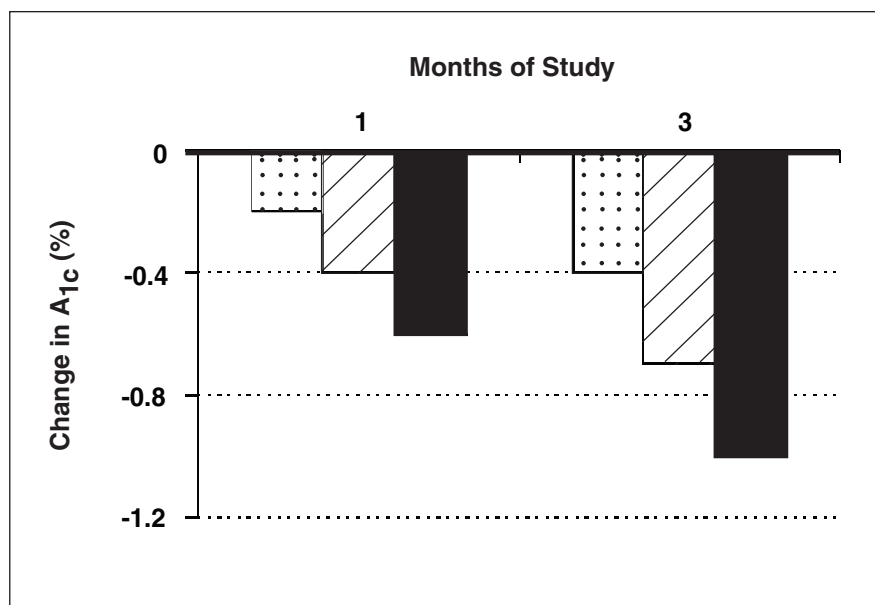


Figure 3. Mean reduction in A1C among 156 patients with poorly controlled diabetes who used no CGM (stippled bars), intermittent CGM (hatched bars), or continuous CGM (solid bars) for a 3-month period. Adapted from Ref. 15.

collected. Based on this information, therapy can be adjusted or precautions taken to prevent hyperglycemia or hypoglycemia. Subsequent follow-up visits can be arranged as needed. Typically, patients should interact with their diabetes health professional at least every 3 months. Patients may need to be reminded that SMBG remains essential for safe and effective use of the CGM device and to help guide treatment decisions.

Efficacy

Does CGM result in improved glucose control and reduced A1C levels?

A pediatric study by the DirectNet Study Group demonstrated a reduction in A1C from $7.1 \pm 0.6\%$ to $6.8 \pm 0.7\%$ ($P = 0.02$) among 30 type 1 diabetic adolescents who used the

Navigator CGM system for 13 weeks after a 1-week period of blinded use.¹² Another study by the same group compared use of the MiniMed CGM system with an eight-point capillary blood glucose determination profile over 3 days among a group of 200 children with type 1 diabetes.¹³ Apart from demonstrating that only 10% of patients complied with the rigorous eight-point capillary testing protocol, this study demonstrated that CGM tended to overestimate the occurrence of overnight hypoglycemia when compared with eight-point capillary determination and that CGM values were generally lower than CBG values (183 ± 37 vs. 183 ± 41 mg/dl; $P = 0.009$). The associations of CGM and capillary blood glucose with A1C were similar and modest in this short-term study ($r = 0.40$ and 0.39 , respectively).

In a randomized, multicenter study of 91 subjects with insulin-requiring diabetes by Garg et al.,⁵ patients were assigned to wear a DexCom STS system while being either blinded or unblinded to their real-time glucose data. Patients who were unblinded exhibited reduced variability in their daily glycemic excursions, as well as a 21% reduction in the amount of time spent hypoglycemic (< 55 mg/dl), a 23% reduction in the amount of time spent hyperglycemic (> 240 mg/dl), and a 26% increase in the amount of time spent in the target glucose range (81–140 mg/dl) compared to the group who remained blinded to their CGM data. In a similar study of 80 patients who used a DexCom CGM system for three consecutive 7-day periods, the investigators demonstrated that normal mean glucose concentrations (90–130 mg/dl) between midnight and 7:00 a.m. were associated with an A1C level of $< 6\%$.¹⁴ Importantly, this study also reported a striking degree of accuracy for CGM as compared with capillary blood glucose measurement. Specifically, more than 97% of 6,619 paired capillary-CGM data points fell within the acceptable Clarke error grid regions A and B.

Finally, one important study has demonstrated that use of CGM improves A1C in patients with poorly controlled type 1 diabetes.¹⁵ In this study, 81 children and 81 adults on intensive insulin therapy with baseline A1C $> 8.1\%$ (average A1C = 9.6%) were randomized to practice 1) continued SMBG without CGM, 2) CGM for 3 days every 2 weeks, or 3) CGM for a 3-month period. The device employed was the MiniMed Guardian RT, and, as shown in Figure 3, patients who received CGM showed a significant decrease in A1C compared to those who did not. This study shows that patients need not use CGM continuously to experience a benefit from it, that the benefits of CGM on A1C are realized within 1 month, and that both children and adults can benefit from using CGM.

Limitations

All currently available CGM devices measure interstitial glucose. The lag time between when systemic glucose concentration changes appear in the blood and when they appear in the interstitial fluid has been estimated to be between 4 and 26 minutes. This lag results from a delay in equilibration

Table 2. CGM Internet Resources

- DexCom STS. DexCom, Inc., Homepage. <http://www.dexcom.com/index.html>.
- MiniMed CGM System Gold. Medtronic Homepage. <http://www.minimed.com/professionals/products/cgms/features.html>.
- MiniMed CGM System Guardian. Medtronic Homepage. <http://www.minimed.com/professionals/products/guardian/components.html>.
- Freestyle Navigator CGM System. Abbott Diabetes Care Homepage. www.abbottdiabetescare.com/adc_dotcom/url/content/en_US/10.10:10/general_content/General_Content_0000163.htm.
- Paradigm REAL-Time and Guardian REAL-Time Systems. FDA Homepage. www.fda.gov/cdrh/mda/docs/p980022s015.html.
- DexCom STS CGM System. FDA Homepage. <http://www.fda.gov/cdrh/mda/docs/p050012.html>.

between blood and interstitial glucose and limits the accuracy of CGM for predicting blood glucose concentrations (especially when these concentrations are changing rapidly). The nonlinear nature of the lag has made surmounting this limitation difficult. All CGM devices require calibration with plasma glucose at least twice a day, with studies showing improved accuracy with increased numbers of calibrations. Additionally, some studies suggest that accuracy improves when calibrations are performed during times of relative glucose stability rather than during periods when the glucose concentration is rapidly changing.

The overestimation of hypoglycemia observed in a number of studies may render CGM inconvenient for people who experience frequent bouts of hypoglycemia, but the technology can also be a very useful tool for people who suffer from hypoglycemia unawareness. In such patients, the lower alarm setting should be chosen carefully so as not to incur too many false alerts while still allowing enough time to verify that blood glucose values are actually low before acting to correct the hypoglycemia. For this reason, it is argued that trends may be more useful than the absolute value reported. All CGM devices provide information regarding the trend of glucose, indicated by an up or down arrow or by a graphic representation of glucose concentrations over time. These indicators of trend, used together with the point measurements of interstitial glucose, provide the means by which patients can reduce the number and duration of hypoglycemic episodes.

The overestimation of hypoglycemia (and to a lesser extent, hyperglycemia) limits the utility of the current generation of CGM devices from working in a “closed-loop” insulin pump system. The idea of a closed-loop system, or artificial pancreas, has long been a goal of many researchers. The rapid development of small, portable CGM devices during the past decade has led many to consider that a closed-loop system may soon be possible. Problems arise, however, when attempting to employ currently available insulin pumps with CGM devices to create a closed-loop system. For an efficient closed-loop system to respond appropriately to a meal, the device would first have to detect a rise in interstitial glucose, which is delayed by at least 10 minutes. This lag

needs to be added to the delay in insulin delivery and absorption that occurs with any subcutaneous insulin. These factors, combined with the imprecise accuracy of CGM, significantly reduce the feasibility of using these devices in a closed-loop system.

Is CGM technology covered by health insurance plans?

The costs for CGM are substantial and are currently a major barrier to its widespread use. The initial expenditure for a CGM device varies from \$400 to > \$2,000. Moreover, the cost of the disposable sensors, which last between 3 and 7 days, as well as the cost of the glucose test strips used to calibrate the sensors, amounts to additional substantial monthly costs to patients, sometimes exceeding \$200 per month. Additionally, the FDA approval for these devices requires the use of capillary blood glucose determination before treatment decisions are made. Using the DexCom STS system as an example, the starter kit (which includes a receiver, transmitter, two sensors and applicators, a carrying case, and a recharger) costs ~ \$400. A 1-month supply of sensors costs an additional \$240. Adding the cost of capillary glucose test strips, the total monthly cost may exceed \$300. Private insurance payers provide coverage only on a case-by-case basis. On the other hand, these costs are easily justified by the avoidance of one emergency hospital visit or one automobile accident per year. One also needs to appreciate the savings in lives and property that may occur by the avoidance of severe hypoglycemia.

To obtain insurance coverage for CGM, physicians often need to play a strong role in assisting patients by writing letters of necessity, describing the overall diabetes care plan (including CGM), and certifying that care management will occur while the patient is on CGM. Patients should also be encouraged to contact the manufacturer’s customer service representative, who may be able to assist in getting coverage. Both patients and providers should be prepared to appeal the case, often multiple times. The Juvenile Diabetes Research Foundation has helpful information on its website (www.JDRF.org), outlining the process for case-by-case CGM coverage.

Medicare and Medicaid have not yet agreed to cover CGM costs. As of January 2008, there are Medicare and Medicaid service codes available for CGM providers, which may signal an improved likelihood of reimbursement in the future. Improved technology resulting in greater accuracy and usability may also enhance the acceptance of CGM technology by practitioners, thereby increasing the demand for insurance coverage. Improvements in the sensor technology aimed at increasing sensor life span may further reduce costs. Providers should also remember that CGM devices do not need to be worn continuously to confer benefit, and although the glycemic benefit is not as great as when CGM is worn continuously, the cost for sensors can be reduced by wearing the CGM intermittently rather than continuously.

Special Populations

The use of CGM in specific populations of patients requires comment. The benefit of CGM depends to a great extent on its limitations, such as the complexity of its use and its relatively reduced sensitivity at low blood glucose concentrations. On the other hand, trend data can be very useful for avoiding hypo- and hyperglycemia. The most obvious populations of candidates for CGM are adult type 1 diabetic patients who are attempting to improve their glucose control and avoid severe hypoglycemia. Children with type 1 diabetes are also good candidates as long as they are able to master the technology, which requires frequent SMBG. If the child is able to master intensive insulin therapy and an insulin pump, then CGM is likely to be a feasible option, although it does put an added burden on patients. Type 2 diabetic patients are also candidates for CGM, especially those who are insulin-dependent and who experience hypoglycemia. For type 2 diabetic patients who are on oral therapy and who rarely have hypoglycemia, CGM does not yet offer a significant advantage.

CGM can be helpful anytime glucose control is important. Recent data have suggested improved outcomes in the intensive care unit when blood glucose is normalized. CGM is currently being evaluated as an adjunct for this group of patients

and may prove beneficial. A final group of individuals who benefit from CGM are those who may be classified as “brittle.” Many of these individuals do many capillary blood glucose determinations each day because of frequent changes in their blood glucose concentrations. We have found that these individuals can actually reduce the frequency of SMBG because CGM provides them with feedback about their glucose concentration every 5 minutes. For one of our patients who used to be in the hospital emergency room approximately once per week with severe hypoglycemia, his visits have all but stopped because of the hypoglycemia warning that CGM provides. For this individual, CGM has been truly lifesaving.

Summary and Conclusions

The American Diabetes Association has taken a very limited position regarding CGM, stating that, “Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose (SMBG) for selected patients with type 1 diabetes, especially those with hypoglycemia unawareness.”¹⁶ It is certain that this statement will be expanded in the future.

Our position on CGM is that this new technology can offer diabetic patients a major advance in improving A1C values and reducing the occurrence of disruptive hypoglycemia. Although the long-term danger of hyperglycemia is an increase in diabetes complications, the short-term hazard of hypoglycemic unawareness can be devastating. An automobile accident, a fall resulting in fracture, or a death from severe hypoglycemia is reason enough to consider using CGM.

There is no doubt that CGM technology will continue to improve, just as has occurred with insulin pump technology during the past 20 years. We believe, however, that it would be a mistake to wait for these improvements. We encourage all of our diabetic patients who experience

hypoglycemia to consider purchasing a CGM system. We hope that medical insurance companies will soon realize the savings in property and lives and routinely cover the cost of this advance in technology.

References

- ¹Hanaire H: Continuous glucose monitoring and external insulin pump: towards a subcutaneous closed loop. *Diabetes Metab* 32:534–538, 2006
- ²Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P: A pilot study of the continuous glucose monitoring system. *Diabetes Care* 24:2030–2034, 2001
- ³Klonoff DC: A review of continuous glucose monitoring technology. *Diabetes Technol Ther* 7:770–775, 2005
- ⁴Bode BW, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastroianni J: Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the Guardian continuous monitoring system. *Diabetes Technol Ther* 6:105–113, 2004
- ⁵Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S, Jovanovic L: Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 29:44–50, 2006
- ⁶Feldman B, Bragg R, Schwartz S, Weinstein R: A continuous glucose sensor based on wired enzyme technology: results from 3-day trial in patients with type 1 diabetes. *Diabetes Technol Ther* 5:769–799, 2003
- ⁷Buckingham BA, Kollman C, Beck R, Kalajian A, Fiallo-Scharer R, Tansey MJ, Fox LA, Wilson DM, Weinzimer SA, Ruedy KJ, Tamborlane WV, DirectNet Study Group: Evaluation of factors affecting CGMS calibration. *Diabetes Technol Ther* 8:318–325, 2006
- ⁸Melki V, Ayon F, Fernandez M, Hanaire-Broutin H: Value and limitations of the continuous glucose monitoring system in the management of type 1 diabetes. *Diabetes Metab* 32:123–129, 2006
- ⁹Bode BW, Schwartz S, Stubbs HA, Block JE: Glycemic characteristics in continuously monitored patients with type 1 and type 2 diabetes: normative values. *Diabetes Care* 28:2361–2366, 2005
- ¹⁰Klonoff DC: Continuous glucose monitoring. *Diabetes Care* 28:1231–1239, 2005
- ¹¹Edelman SV, Bailey TS: *CGM Guide: Continuous Glucose Monitoring*. San Diego, Calif., DexCom, Inc., 2007
- ¹²Buckingham B, Beck RW, Tamborlane WV, Xing D, Kollman C, Fiallo-Scharer R, Mauras N, Ruedy KJ, Tansey M, Weinzimer SA, Wysocki T, DirectNet Study Group: Continuous glucose monitoring in children with type 1 diabetes. *J Pediatr* 151:388–393, 2007
- ¹³Fiallo-Scharer R; Diabetes Research in Children Network Study Group: Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab* 90:3387–3391, 2005
- ¹⁴Garg S, Jovanovic L: Relationship of fasting and hourly blood glucose levels to HbA1c values: safety, accuracy, and improvements in glucose profiles obtained using a 7-day continuous glucose sensor. *Diabetes Care* 29:2644–2649, 2006
- ¹⁵Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M: Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 29:2730–2732, 2006
- ¹⁶American Diabetes Association: Standards of medical care in diabetes—2008. *Diabetes Care* 31 (Suppl. 1):S12–S54, 2008

Additional Selected Readings

- Chase HP, Kim LM, Owen SL, MacKenzie TA, Klingensmith GJ, Murtfeldt R, Garg SK: Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics* 107:222–226, 2001
- DirectNet Study Group. Evaluation of factors affecting CGMS calibration. *Diabetes Technol Ther*;8:318–325, 2006
- Goldberg PA, Siegel MD, Russell RR, Sherwin RS, Halickman JJ, Cooper DA, Dziura JD, Inzucchi SE: Experience with the continuous glucose monitoring system in a medical intensive care unit. *Diabetes Technol Ther* 6:339–347, 2004
- Guerci B, Floriot M, Bohme P, Durain D, Benichou M, Jellimann S, Drouin P: Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. *Diabetes Care* 26:582–589, 2003

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