Continuous Glucose Monitoring

Roadmap for 21st century diabetes therapy

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Continuous glucose monitoring provides maximal information about shifting blood glucose levels throughout the day and facilitates the making of optimal treatment decisions for the diabetic patient. This report discusses continuous glucose monitoring in terms of its purposes, technologies, target populations, accuracy, clinical indications, outcomes, and problems. In this context, the medical literature on continuous glucose monitoring available through the end of 2004 is reviewed.

PURPOSES — Continuous glucose monitoring provides information about the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels. Compared with conventional intensified glucose monitoring, defined as three to four blood glucose measurements per day, continuous monitoring provides much greater insight into glucose levels throughout the day. Continuous glucose readings that supply trend information can help identify and prevent unwanted periods of hypo- and hyperglycemia.

The difference between an intermittent and a continuous monitor for monitoring blood glucose is similar to that between a regular camera and a continuous security camera for monitoring an important situation. A regular camera takes discrete, accurate snapshots; its pictures do not predict the future; it produces a small set of pictures that can all be carefully studied; and effort is required to take each picture. A continuous security camera, on the other hand, takes multiple, poorly focused frames; displays a sequential array of frames whose trend predicts the future; produces too much information for each frame to be studied carefully; and operates automatically after it is turned on. The two types of blood glucose monitors differ in much the same way: *1*) an intermittent blood glucose monitor measures discrete glucose levels extremely accurately, whereas a continuous monitor provides multiple glucose levels of fair accuracy; *2*) with an intermittent monitor, current blood glucose levels do not predict future glucose levels, but with a continuous monitor, trends in glucose levels do have this predictive capability; *3*) with an intermittent monitor, it is easy to study every measured blood glucose value over most time periods, but with a continuous monitor, too many data are generated to study all data points; and *4*) an intermittent blood glucose monitor requires effort to operate, whereas a continuous monitor does not. Returning to the camera analogy, just as the best tool for closely monitoring a situation when the outcome is important often may be a continuous security camera rather than a regular camera, likewise the best way to monitor diabetes often may be a continuous glucose monitor (CGM) rather than an intermittent monitor.

TECHNOLOGIES — Five CGMs have been approved by the U.S. Food and Drug Administration (FDA) for use in the U.S. or carry CE marking for use in Europe. They are the Continuous Glucose Monitoring System Gold (CGMS Gold; Medtronic MiniMed, Northridge, CA) (1), the GlucoWatch G2 Biographer (GW2B; Cygnus, Redwood City, CA) (2), the Guardian Telemetered Glucose Monitoring System (Medtronic MiniMed) (3), the GlucoDay (A. Menarini Diagnostics, Florence, Italy) (4), and the Pendra (Pendragon Medical, Zurich, Switzerland) (5). A sixth monitor, whose premarket approval application has been submitted to the FDA, is the FreeStyle Navigator Continuous Glucose Monitor (Abbott Laboratories, Alameda, CA) (6).

The currently available CGMs measure blood glucose either with minimal invasiveness through continuous measurement of interstitial fluid (ISF) or with the noninvasive method of applying electromagnetic radiation through the skin to blood vessels in the body. The technologies for bringing a sensor into contact with ISF include inserting an indwelling sensor subcutaneously (into the abdominal wall or arm) to measure ISF in situ or harvesting this fluid by various mechanisms that compromise the skin barrier and delivering the fluid to an external sensor (7). These ISF measurement technologies are defined as minimally invasive because they compromise the skin barrier but do not puncture any blood vessels. After a warm-up period of up to 2 h and a device-specific calibration process, each device's sensor will provide a blood glucose reading every 1–10 min for up to 72 h with the minimally invasive technology and up to 3 months with the noninvasive technology. Results are available to the patient in real time or retrospectively. Every manufacturer of a CGM produces at least one model that sounds an alarm if the glucose level falls outside of a preset euglycemic range. The available and likely soon-to-be-available CGMs are compared in Table 1.

Based on their mechanisms, specifications, and performance records, each CGM offers a particular set of features that are attractive for patients and clinicians. Table 2 presents three of these features for each available and likely soon-to-be-available CGM.

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Abbreviations: CGM, continuous glucose monitor; CGMS, continuous glucose monitoring system; EGA, error grid analysis; FDA, U.S. Food and Drug Administration; GW2B, GlucoWatch G2 Biographer; ISF, interstitial fluid; ISO, International Organization for Standardization; RAD, relative absolute difference.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Specifications of available and likely soon-to-be-available products for continuous glucose monitoring*

Product	FDA approved	CE marked	Year first approved or marked	Sensor type	Sensor mechanism	Sensor location	Sensor warmup (h)	Calibrations per lifetime of sensor	Sensor lifespan (h)	Frequency of testing (min)	Time of blood glucose data display	Alarm
Continuous Glucose Monitoring System Gold	Yes	Yes	1999	Minimally invasive	Enzyme-tipped catheter	Subcutaneous abdomen	2	12	72	5	Retrospective	No
GlucoWatch G2 Biographer	Yes	Yes	2001	Minimally invasive	Reverse iontophoresis	External on arm or forearm	2	1	13	10	Real time	Yes
Guardian Telemetered Glucose Monitoring System	Yes	Yes	2004	Minimally invasive	Enzyme-tipped catheter	Subcutaneous arm	2	12	72	5	Retrospective	Yes
GlucoDay	No	Yes	2001	Minimally invasive	Microdialysis	Subcutaneous abdomen	0	1	48	3	Real time or retrospective	Yes
Pendra	No	Yes	2004	Noninvasive	Impedance spectroscopy	External on wrist	1	20	3 months	1	Real time	Yes
FreeStyle Navigator Continuous Glucose Monitor	No	No	—	Minimally invasive	Enzyme-tipped catheter	Subcutaneous arm	1	1	72	1	Real time	Yes

Invasive indwelling intravascular sensors that measure blood glucose directly are also under development for monitoring hospitalized patients. Prolonged use of such devices might cause vascular damage or infection. No articles have been published on their performance.

TARGET POPULATIONS—Proper patient selection will ensure safe use of CGMs. Patients should be motivated to participate in their diabetes care, informed about diabetes, and mechanically adept. These characteristics are even more necessary for real-time than for retrospective monitors. Currently available CGMs require up to four finger-stick (not alternate site) blood glucose measurements per day for calibration. The ideal time to calibrate is either after fasting or at least 3 h postprandially, but not right after exercise or when the blood glucose level is likely to be rising or falling. Without such calibration, continuous readings may be inaccurate. Currently available CGMs that provide real-time readings should not be used to make therapeutic decisions, such as whether to dose insulin or eat, because they are not sufficiently accurate. Instead, an abnormal reading should prompt a finger-stick blood glucose measurement whose value can be acted upon. Patients require a thorough training program to calibrate and operate a CGM. Furthermore, patients using real-time CGMs require extensive diabetes education to make safe and effective therapeutic decisions. In particular, they must know the duration of their boluses of insulin to avoid repeatedly and excessively injecting themselves with unnecessary extra doses of insulin over a short duration for hyperglycemia that does not immediately respond to the first insulin dose.

The second-generation CGMS Gold and its first-generation predecessor, CGMS, together have been studied in the greatest number of articles about continuous glucose monitoring in the medical literature. A CGM can be used to evaluate 24-h blood glucose profiles in diabetic patients who are receiving glucose-lowering drugs. Using Medtronic MiniMed's CGMS, Levetan et al. (8) and Abrahamian et al. (9) quantified the effect of pramlintide and nateglinide on blood glucose, respectively.

Table 2—*Attractive features of available and likely soon-to-be-available continuous glucose monitors*

Model	Features
Continuous Glucose Monitoring System Gold	Long sensor life Avoids arm implantation First product on the market and used in the most studies
GlucoWatch G2 Biographer	Needle-free Real-time readings Alarm for out-of-range values
Guardian Telemetered Glucose Monitoring System	Long sensor life Alarm for out-of-range values Avoids arm implantation
GlucoDay	Real-time readings Infrequent calibrations Choice of retrospective or real-time data
Pendra	Noninvasive No skin irritation Measures glucose in blood and not in interstitial fluid
FreeStyle Navigator Continuous Glucose Monitor	Long sensor life Alarm for out-of-range values Avoids abdominal wall implantation

ACCURACY — A real-time CGM can be programmed to sound an alarm for readings below or above a target range (10). The most important use of an alarm is to detect unsuspected hypoglycemia (such as during sleep) so that glucose can be administered to prevent brain damage. There is a trade-off between an alarm's sensitivity and specificity. In general, if the alarm is set to sound at a lower level than the hypoglycemic threshold, then the specificity will be good but the sensitivity may be poor. If the alarm is set to sound at a glucose level higher than the hypoglycemic threshold, then the sensitivity will be good but the specificity may be poor. The greater accuracy a continuous monitor can provide, the less of a trade-off is necessary (11).

The Diabetes Research in Children Network (DirecNet) is a U.S. network of five clinical centers and a coordinating center dedicated to researching glucose monitoring technology in children with type 1 diabetes (12). The network's investigators, the DirecNet Study Group, assessed the accuracy of the first- and second-generation CGMS and the GW2B in children with type 1 diabetes in concurrently published studies (13,14). The second-generation CGMS Gold, compared with the first-generation CGMS, had a lower median relative absolute difference (RAD) between CGMS glucose and reference serum glucose paired values (11 and 19%, respectively) (13). For the GW2B, the median RAD between GW2B glucose and reference serum glucose paired values was 16% (14). Similar RAD values of 21% have been reported for the first-generation CGMS by Kubiak et al. (15). RAD values of 12.8% (16) and 12.8–15.7% (17) have been reported for the second-generation CGMS Gold system by Goldberg et al. (16) and Guerci et al. (17), respectively.

Djakoure-Platonoff et al. (18) evaluated CGMS accuracy in 53 type 1 diabetic inpatients and outpatients who wore a CGMS for 3–6 days. The mean absolute differences between sensor and blood glucose meter values were 25–34 mg/dl.

Maran et al. (4), using the GlucoDay CGM, observed that for a mixed type 1/type 2 diabetic population, the percent bias between the GlucoDay and venous blood levels was −2.0% in the hypoglycemic range (<70 mg/dl), 6.9% in the euglycemic range (70–180 mg/dl), and 11.2% in the hyperglycemic range (>180 mg/dl). Poscia and colleagues found the GlucoDay RAD to be 20% in rabbits (19) and 15% in a mixed type 1/type 2 diabetic population (20).

Bode et al. (3) evaluated the performance of the Guardian Continuous Monitoring System (Medtronic MiniMed) and whether using real-time alarms reduced hypo- and hyperglycemic excursions in a type 1 diabetic population. The mean absolute relative error between home blood glucose meter readings and sensor values was 21.3% (median 7.3%); further, on average the Guardian read 12.8 mg/dl below the concurrent home blood glucose meter readings. The hypoglycemia alert was able to distinguish glucose values ≤70 mg/dl with 67% sensitivity, 90% specificity, and 47% false alerts. The hyperglycemia alert showed a similar ability, detecting values ≥250 mg/dl with 63% sensitivity, 97% specificity, and 19% false alerts. The alerts resulted in a significant ($P = 0.03$) reduction in the duration of hypoglycemic excursions and a marginally significant ($P = 0.07$) increase in the frequency of hyperglycemic excursions.

The DirecNet Study Group (21) found the CGMS Gold system, which is the second generation of CGMS technology, as well as the GW2B, which is the second generation of GlucoWatch technology, to have inversely proportional sensitivity and specificity rates during hypoglycemia in children and adolescents with type 1 diabetes. A series of alarm settings were selected for a reference blood glucose of 60 mg/dl. For CGMS Gold, the settings with sensitivity and specificity were 60 mg/dl, 49 and 42%; 80 mg/dl, 84 and 36%; 100 mg/dl, 100 and 25%; and 120 mg/dl, 100 and 16%. With the GW2B, the settings were 60 mg/dl, 23 and 49%; 80 mg/dl, 59 and 33%; 100 mg/dl, 84 and 20%; and 120 mg/dl, 92 and 15%. The authors concluded, "These data show that the GW2B and the CGMS do not reliably detect hypoglycemia. Both of these devices perform better at higher glucose levels, suggesting that they may be more useful in reducing HbA_{1c} levels than in detecting hypoglycemia" (21).

Tsalikian et al. (22) observed the sensitivity and specificity of the hypoglycemic alarm and the down alert alarm on the GW2B in 89 children and adolescents with type 1 diabetes. The "down alert" alarm is triggered when extrapolation of the current glucose trend anticipates that hypoglycemia will occur within the next 20 min. Overnight sensitivity was 23% with the hypoglycemia alarm alone and 77% when combined with the down alert alarm. For the hypoglycemia alarm alone, the false-positive rate was 16%, but for the two alarm types combined, the false-

positive rate increased to 62%. The down alert alarm improved the sensitivity of the GW2B to detect hypoglycemia but resulted in a large increase in the false alarm rate.

Conrad et al. (23) evaluated the sensitivity and specificity of the CGMS for reference capillary blood glucose levels <60 mg/dl in five children and infants with hypoglycemic disorders. They reported a sensitivity of 65%, a specificity of 91%, and a false-positive rate of 43%.

The International Organization for Standardization (ISO) standards for accuracy of point blood glucose tests require that a sensor blood glucose value be within 15 mg/dl of reference for a reference value ≤75 mg/dl and within 20% of reference for a reference value >75 mg/dl. Sensor accuracy by this definition is expressed as the percentage of data pairs meeting these requirements (24). The DirecNet group found that for hypoglycemic blood glucose levels (determined by a reference blood glucose monitor, the OneTouch Ultra), the CGMS Gold met the ISO standards in only 48% of readings and the GW2B met these standards in only 32% of readings (13,14). The percentage of data points attaining ISO accuracy standards climbed as the blood glucose level rose, topping out for the highest segment of reference blood glucose levels (i.e., blood glucose values ≥240 mg/dl). In this glycemic category, the CGMS Gold and GW2B, respectively, met ISO accuracy for 81 and 67% of data points (13,14). In a separate series of 15 healthy nondiabetic children undergoing continuous glucose monitoring over 24 h, the DirecNet Group reported that the median absolute difference in concentrations for the GW2B was 13 mg/dl and for the CGMS was 17 mg/dl. Furthermore, 30% of the values from the GW2B and 42% of the values from the CGMS deviated by >20 mg/dl from the reference value (25).

The DirecNet investigators also noted that the second-generation CGMS (CGMS Gold) devices that they tested performed better than first-generation CGMS devices (21). The second-generation algorithm had previously been reported to be more useful for avoiding false hypoglycemic and hyperglycemic readings in nondiabetic children, whereas both algorithms gave similar results in diabetic children (26). The overreading of nocturnal hypoglycemia with the first-generation CGMS devices had been suspected because of both a high incidence of asymptomatic nocturnal hypoglycemia reported by the CGMS (without simultaneous blood glucose monitor readings) in children with type 1 diabetes (27–29) and documented spurious hypoglycemic readings (30,31). The sensor malfunction rate of 18–28% (31–33) in the first-generation CGMS sensors has been improved in the second-generation CGMS Gold system; a malfunction rate of 17–18% has been reported in two series of CGMS Gold users (16–17).

Kovatchev et al. (34) have proposed a continuous glucose error grid analysis (EGA) system for analyzing the performance of CGMs. This tool is an updated version of the EGA that was developed to assess the performance of intermittent blood glucose monitors (35). The continuous glucose EGA combines a point-EGA (p-EGA; corrected for time lags between fluctuations in ISF and blood during dynamic fluctuations in circulating glucose levels) with a rate EGA (r-EGA). The continuous glucose EGA classifies readings of combined p-EGA and r-EGA as "accurate," "benign," or "erroneous." The use of r-EGA fine-tunes the assessment of accuracy compared with the use of p-EGA only. The continuous glucose EGA can judge the performance of a CGM separately at low, normal, and high blood glucose levels.

The mean blood glucose level measured by a CGMS over 72 h correlates, to some extent, with a patient's HbA_{1c} level, which reflects the mean blood glucose level over the previous 1–4 months (36). A correlation between mean sensor glucose value, determined by CGMS, and the HbA_{1c} value has been observed to be $r = 0.53$ ($P = 0.002$) (37) and $r = 0.59$ ($P = 0.002$) (38).

CLINICAL INDICATIONS

— Situations that require detailed information about blood glucose fluctuations that only continuous monitoring can provide include when adjusting therapy, quantifying the response in a trial of a diabetes therapy, assessing the impact of lifestyle modifications on glycemic control, monitoring conditions where tighter control without hypoglycemia is sought (e.g., gestational diabetes, pediatric diabetes, in the intensive care unit), diagnosing and then preventing hypoglycemia (e.g., during sleep, with hypoglycemia unawareness), and diagnosing and preventing postprandial hypoglycemia. The most important use of continuous blood glucose monitoring is to facilitate adjustments in therapy to improve control. Specific therapeutic adjustments include changing from regular to a synthetic ultrashort-acting insulin analog at mealtime, changing from NPH to a synthetic ultralong-acting insulin once or twice per day, increasing or decreasing the mealtime insulin bolus dosage, increasing or decreasing the basal insulin rate, altering the treatment of intermittent hypoglycemia or hyperglycemia, changing the insulin-to-glucose correction algorithm for premeal hyperglycemia, changing the insulin-to-carbohydrate ratio at mealtime, changing the method for counting carbohydrates, changing the carbohydrate composition of the diet, changing the discount in short-acting insulin dosage for exercise, changing the nighttime regimen because of the dawn phenomenon, changing the target preprandial or postprandial blood glucose values, or before referring a patient for psychological counseling to improve adherence to the treatment regimen.

The most frequent therapy adjustment by Sabbah et al. (39) (out of eight adjustments) was to increase the mealtime bolus dosage. The most frequent therapy adjustment by Kaufman et al. (40) (out of nine adjustments) was to modify the type of basal long-acting insulin.

OUTCOMES

— Of five randomized controlled studies of CGM technologies that have used HbA_{1c} as a surrogate marker for morbidity and mortality related to diabetes (27,41–44), four evaluated the CGMS (27,42–44) and one evaluated the GW2B (41). In each study, the use of continuous glucose monitoring compared with standard monitoring was associated with improved mean HbA_{1c} levels.

Chase et al. (27) in 2001 reported a 1-month randomized, controlled pilot trial of the CGMS in 11 children as a supplement to standard capillary blood glucose monitoring to improve HbA_{1c}. The CGMS group experienced a statistically significant decrease in mean HbA_{1c} of 0.36% ($P < 0.01$), whereas the control subjects experienced a nonsignificant decrease in HbA_{1c} of 0.2%. The difference between changes in the two groups was 0.16%, which is not a very important difference in such a small study. At 3 months

(2 months postintervention), four of the five children who used the CGMS continued to have lower (but no longer significantly lower) HbA_{1c} values in comparison with their initial values (mean decrease for the group of five CGMS users = 1.04%; $P = 0.07$); three of the six control participants also had lower HbA_{1c} values at 3 months (mean decrease for the group of six control subjects = 0.62%).

In a 2003 study, Chase et al. (41) reported that compared with standard therapy, the GlucoWatch Biographer significantly improved glucose control. They randomly assigned 40 children to diabetes management with or without the GlucoWatch Biographer. Both groups performed conventional blood glucose monitoring four times per day. Subjects in the Biographer group used the Biographer for 3 months (intervention phase) and were then followed for an additional 6 months (observational phase). Biographer wearers were asked to check their blood glucose reading if the Biographer glucose reading was ≤70 or ≥300 mg/dl. After 3 months, HbA_{1c} values improved from 8.9 at baseline to 8.4% in Biographer users and worsened from 8.6 to 9.0% in control subjects. The difference between Biographer users and control subjects (8.4 vs. 9.0%; $P < 0.05$) at 3 months was statistically significant. During the observation phase following the intervention phase, the HbA_{1c} in the Biographer group remained lower than in the control group (at months 6 and 9 of the study), but the differences were no longer statistically significant.

Chico et al. (42) in 2003 reported on the results of a 3-month randomized, controlled trial of 75 type 1 diabetic subjects who were treated with the CGMS (40 subjects in the treatment group) or intensive capillary glucose measurement (35 subjects in the control group) (42). HbA_{1c} concentrations decreased significantly in both the CGMS (from 8.3 to 7.5%; $P < 0.01$) and the control (from 8.0 to 7.5%; $P < 0.01$) groups. However, the CGMS did not result in statistically better outcomes compared with capillary glucose measurements.

In 2003, Ludvigsson and Hanas (43) reported on the results of a controlled, crossover trial comparing the effect of using a CGMS or seven-point glucose profiles on HbA_{1c}. During the open arm of the trial, the 27 type 1 diabetic subjects wore the CGMS for 3 days every 2 weeks for 3 months, and during the blinded (to CGMS data) arm, the subjects checked seven-point glucose profiles every week for 3 months. At 3 months, the two study arms were crossed over. The HbA_{1c} levels decreased significantly in the open arm using the CGMS (from 7.70 to 7.31%; $P = 0.013$), but not in the blinded arm (7.75 to 7.65%; NS); the difference between study arms was significant (7.31 vs. 7.65%; $P = 0.011$).

In 2004, Tanenberg et al. (44) reported on a 12-week trial comparing CGMS with standard glucose monitoring in 128 insulin-treated diabetic subjects. In both groups, the HbA_{1c} levels decreased significantly compared with baseline values, but there was a nonsignificant improvement in HbA_{1c} outcomes in the CGMS group compared with the standard monitoring group. HbA_{1c} levels decreased by 0.8% in the CGMS group and 0.7% in the standard group ($P = 0.70$). The CGMS group, however, had a significantly shorter mean duration of hypoglycemic events (sensor glucose ≤ 60 mg/dl) at week 12 of the study (49 vs. 81 min; $P = 0.009$).

An additional five nonrandomized, uncontrolled trials of continuous glucose monitoring have demonstrated a statistically significant improvement in HbA_{1c} using this technology in addition to usual capillary blood glucose monitoring (37,40,45–47). The studies are discussed below.

In 1999, Bode et al. (45) reported the first pilot study of the clinical performance of the CGMS in an uncontrolled, nonrandomized trial of nine type 1 diabetic subjects. After a pair of 1-week courses of monitoring followed by therapeutic adjustments based on CGMS readings, mean HbA_{1c} levels fell from 9.9 at baseline to 8.8% ($P = 0.0006$) within 5 weeks of the trial's commencement. The improved HbA_{1c} levels were sustained: 10 weeks into the study, the mean HbA_{1c} of this population had further declined to 8.6% ($P = 0.019$) (48).

Kaufman et al. (40) reported in 2001 on an uncontrolled, nonrandomized study of the effect on HbA_{1c} of a single 72-h course of CGMS monitoring in a cohort of 47 pediatric subjects. The continuous information was used to alter therapy. Mean HbA_{1c} levels fell from 8.6 to 8.4 and 8.3% (both paired Student's t test, $P \leq 0.03$) 3 and 6 months, respectively, after the course of CGMS compared with at the time of placement.

Schiaffini et al. (46) reported in 2002 the findings of a study in which the CGMS was applied on two occasions 6 weeks apart for 72 h per each application. The study was initially conducted on 27 type 1 diabetic children, all of whom received an initial course of CGMS monitoring and 18 of whom elected to continue in the 6-week study to receive therapy adjustments and a second course of CGMS monitoring upon completion of the study. All continuing subjects self-monitored capillary blood glucose levels 4–5 times daily. Insulin therapy was adjusted based on the initial CGMS results and subsequent spot capillary glucose levels. Of the 18 subjects who fully participated in the study, compared with the single CGMS cohort, there was a significant fall in mean serum fructosamine levels from 349 to 330 μmol/l ($P < 0.05$). Study participants completing the study also experienced a decreased number of hypoglycemic events per 72 h compared with the incidence rate among baseline measurements of those not completing the study (2.5 vs. 3.9 episodes per 72 h; $P < 0.05$).

In 2002, Salardi et al. (37) reported on a study of the prolonged effects of a 72-h course of CGMS monitoring in a nonrandomized, uncontrolled trial with 28 type 1 diabetic subjects. The subjects' HbA_{1c} was lower by 0.40 and 0.43% 3 and 6 months, respectively, after the course of CGMS monitoring compared with baseline levels (37).

In 2003, Schaepelynck-Belicar et al. (47) reported the findings of a nonrandomized, uncontrolled trial of a 72-h course of CGMS monitoring. Continuous data were used to determine rational adjustments in insulin therapy in 12 type 1 diabetic subjects. Changes involved alterations of the dosage in three subjects, insulin type in seven subjects, the number of daily injections in five subjects, and the delivery technology (from insulin injection to pump therapy) in one subject. Reassessment 2 months later demonstrated a significant reduction of glycemic excursions in eight subjects and a decrease in the mean HbA_{1c} from 10.3 to 8.75% ($P < 0.05$). The calculated low blood glucose index increased, but not significantly (49).

Continuous glucose monitoring technology has been used as an educational

tool to document the incidence and magnitude of hypoglycemia in diabetic adults (50–52) and children (22,23,28, 29,53,54), pregnant women with diabetes (55–59), patients after pancreas (60) and islet cell (61–62) transplant, and children with glycogen storage disease (63,64). This technology has similarly been used in hyperglycemia in type 1 diabetic subjects using insulin pump therapy (65,66), type 1 diabetic subjects using insulin injections (67), pregnant women with (55–59,68) and without (68,69) diabetes, gastroparesis patients (70), and cystic fibrosis patients (71). Continuous glucose monitoring has also been used as a therapeutic tool to decrease the incidence and magnitude of hypoglycemia in three studies (46,72,73).

In 2004, Weintrob et al. (72) reported the results of a study that used two 72-h courses of CGMS, 2.5 months apart, to provide information for improving glycemic patterns in a cohort of 23 type 1 diabetic children. Compared with the first CGMS reading, the second reading demonstrated a smaller 24-h area under the curve for hypoglycemia ($P = 0.04$), a shorter duration of nocturnal hypoglycemia ($P = 0.05$), and a tendency for a lower rate of diurnal hypoglycemic events ($P = 0.1$).

In a nonrandomized, uncontrolled multicenter series of 15 type 1 diabetic subjects who were monitored using a long-term, investigational, subcutaneously implanted continuous glucose sensor, Garg et al. (73) reported reduced hyperglycemic and hypoglycemic excursions. A control period (mean 50 days) of being blinded to real-time blood glucose data was followed by a study period (mean 44 days) of access to these data. The subjects spent a median of 47% less time under 60 mg/dl ($P < 0.05$) and 25% less time over 240 mg/dl ($P < 0.05$) during the nonblinded study period compared with during the blinded control period.

PROBLEMS — Currently available CGMs can present problems for users. One major problem is their lack of accuracy for each single data point compared with the accuracy of simultaneous intermittent blood glucose measurements. CGMs are generally least accurate in the hypoglycemic range (74). Because of the accuracy issue, it is necessary to incorporate trend information in using continuous blood glucose data. All real-time CGMs incorporate an arrow that indicates an upward or downward trend. The trend arrow can be set to display minor or major levels of upward or downward trending. A minimally invasive CGM can be associated with side effects related to chronic ISF harvesting. The GW2B has been associated with skin irritation, but this problem can be reduced without affecting the measurement accuracy by pretreating the forearm with a corticosteroid spray (75). The Pendra, which resembles the GW2B, does not harvest fluid from the skin or cause skin irritation. The CGMS rarely causes local discomfort from the implanted catheter; the sensor must be inserted at least 2 in from an insulin infusion site and 3 in from an insulin injection site.

Most currently available outpatient continuous blood glucose monitors do not actually measure the glucose concentration within whole blood, but instead measure the glucose concentration within the ISF compartment. The Pendra measures blood glucose both noninvasively and continuously. Depending on activity or feeding schedules (and especially during periods of rapid blood glucose shifting), equilibration between shifting blood and interstitial fluid glucose levels may lag (76). It is unknown whether sensor site selection can minimize this intercompartmental lag or the lag that can occur during equilibration between arterial and skin capillary blood glucose levels at sites other than the fingertip.

Reimbursement for CGMs by insurance or government payer organizations has been limited. Insurance companies are demanding rigorous scientific evidence about continuous monitoring before they will pay for this technology (77). Their stated reason is that an insufficient number of randomized, controlled trials of these devices has shown a statistically significant decrease in diabetic complications or HbA_{1c} levels, which are accepted as a surrogate marker of long-term blood glucose control (78). Indeed, only five articles have been published describing randomized, controlled trials of continuous glucose monitoring technologies for improving clinical outcomes (27,41–44). In all five studies, continuous monitoring compared with standard monitoring was associated with improved HbA_{1c} levels, but the improvements in HbA_{1c} levels in the continuously monitored subjects were statistically significant in only two (41,43) of these five studies.

Continuous glucose monitoring offers the capability of expressing the frequency and severity of hypoglycemic episodes much more clearly than does intermittent glucose testing. Continuous glucose monitoring also offers the capability of expressing the mean blood glucose value in new ways. The mean blood glucose value can shift quickly with any new treatment, and it is not always practical to wait for months or weeks, respectively, for the HbA_{1c} or fructosamine values to shift. Continuous glucose monitoring can document the time spent in the normal, low, and high ranges, which may be more valuable than a single integrated data point, such as HbA_{1c} or fructosamine. Long-term exposure to midrange glycemia may turn out to be better for avoiding complications than exposure to many upward hyperglycemic spikes and downward hypoglycemic spikes; however, the spikes may cancel out each other in terms of altering the long-term markers. Continuous glucose monitoring can distinguish the two exposures, but long-term markers cannot stratify time spent above and below a particular target. It is possible that a new measure of glycemia, derived from the duration of normal, low, and high readings, could supplement HbA_{1c} as an integrated measure of control. Furthermore, measurements of mean amplitude of glycemic excursions (54), composite hypoglycemic score (62), and lability index (62) could provide information about the tendency for a mean blood glucose level to be comprised of stable or labile data points. For some patients, a decreased amount of glycemic instability alone, even without any improvement in HbA_{1c}, might represent an improved outcome.

CONCLUSIONS — Continuous glucose monitoring offers advantages over intermittent glucose monitoring when glycemic patterns are poorly understood. The information about direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels that can be obtained by continuous glucose monitoring is simply not available with intermittent blood glucose monitoring. When retrospective patterns are needed to adjust therapy or document the state of physiology, CGMs are useful. When real-time recognition of both the absolute

magnitude of glycemia as well as trend patterns are needed, then a real-time CGM provides a wealth of information. Technologies for continuous glucose monitoring require patient education for proper use. During hypoglycemia or periods of rapid fluctuation, values provided by CGMs may be inaccurate. Clinical outcome studies suggest that measures of mean glycemia and hypoglycemic burden both improve with the use of continuous glucose monitoring, but more studies are needed to convince payors to reimburse for this technology. In this data-hungry world, it appears likely that CGMs will eventually become a routine part of diabetes management, initially for patients with difficult-to-control diabetes and eventually for most patients with diabetes. Retrospective reporting will eventually give way to real-time readings, and adjunctive use requiring a confirmatory finger-stick blood test will eventually give way to primary use without the requirement of such confirmation. As methods for minimally invasive and noninvasive continuous monitoring advance, diabetic patients will use this technology more routinely. Data printouts from CGMs will increasingly provide a roadmap for effective diabetes management in the 21st century.

ADDENDUM — After this article was submitted for publication, an additional study was published describing the results of a multicenter, randomized, controlled trial of continuous glucose monitoring (79). In 2005, the DirecNet Study Group reported the results of a 6-month trial comparing GW2B use with standard glucose monitoring in 200 type 1 diabetic subjects ages 7–18 years. Use of the GW2B compared with standard glucose monitoring resulted in no significant difference in glycemic control, but was associated with a nonsignificant trend ($P = 0.10$) toward a greater number of episodes of severe hypoglycemia. Furthermore, six additional articles were also published, following the submission of this article, describing the performance of the CGMS in type 1 diabetes (80), type 2 diabetes (81), pregnancy (82), and both type 1 and type 2 diabetic patients receiving peritoneal dialysis (83); the GlucoDay in type 1 diabetes (84); and an investigational viscometric affinity sensor in type 1 diabetes (85).

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