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CLINICAL APPLICATIONS

Real-Time Continuous Glucose Monitoring in the Clinical Setting: The Good, the Bad, and the Practical

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Abstract

Real-time continuous glucose monitoring (RT-CGM) is the latest technological breakthrough in diabetes care. Despite its limitations of lag time between sensor and blood glucose, the need for calibration, false detection of and failure to detect hypoglycemia, and mild discomfort or skin irritation reported in some users, RT-CGM is a highly beneficial tool that can be used to detect nocturnal or unrecognized hypoglycemia and glycemic variability. This, in turn, can lead to better treatment decisions, which may improve metabolic control and decrease the incidence and progression of diabetes complications. The RT-CGM devices are fairly accurate and easy to use. It is not difficult to establish a clinical RT-CGM program in the office. However, it requires persistence and an understanding of the patient's perspective of using RT-CGM so it can be presented and taught appropriately. This article discusses the benefits and limitations of RT-CGM and establishment of a RT-CGM program in the clinical setting.

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Introduction

There is a vast amount of technology available today to assist with diabetes care. In order to maximize the benefits of this technology, it must be embraced by both clinicians and patients. The latest breakthrough on this front is real-time continuous glucose monitoring (RT-CGM), which allows patients and providers alike to see glucose levels in a real-time format. Continuous glucose monitoring (CGM) has been available since the late 1990s. RT-CGM is more recent. The first real-time system, the DexCom STS™, was approved for use by the Food and Drug Administration (FDA) in March 2006, followed by the Medtronic MiniMed (MM) Guardian® and MM Paradigm® Real-Time system in July 2006 and the FreeStyle Navigator® in March 2008.

Real-time continuous glucose monitoring technology utilizes sensor electrodes, small filaments (<13 mm in length) that are inserted into the subcutaneous tissue with an introducer needle. The sensor electrodes measure glucose in the interstitial fluid (IF) through a glucose oxidase reaction, which converts the glucose level into an electronic signal. This signal is transmitted continuously

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (CPT) Current Procedural Terminology, (DCCT) DiabetesControl and Complications Trial, (DirecNet) Diabetes Research in Children Network, (EDIC) Epidemiology of Diabetes Interventions and Complications, (FDA) Food and Drug Administration, (HbA1c) hemoglobin A1c, (IF) interstitial fluid, (LMN) letter of medical necessity, (MM) Medtronic MiniMed, (RT-CGM) real-time continuous glucose monitoring, (SBGM) self-blood glucose monitoring

Keywords: continuous glucose monitoring, diabetes, glucose sensor, glycemic variability, hypoglycemia, technology

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via radio frequency to the receiver, which converts the electrochemical signal into a glucose reading and displays it for the user. The sensor electrodes are FDA approved to stay in the body for 3–7 days. The system can be programmed to alert the user when glucose levels are too high or too low. Additionally, some systems can alert the user if the glucose is predicted to be outside of the target range in a certain amount of time or if the glucose is changing too rapidly.

Accuracy

A plot of sensor readings on the traditional Clarke error grid has found RT-CGM to be 62.8–88.0% accurate (A+B) in the hypoglycemic range and 96.3–99.0% accurate (A+B) in the euglycemic range.[1,2] Additionally, MM Guardian data found no readings in the failure to detect (D) or dangerous (E) zones on the error grid (data available upon request).

Several new studies reported over the past 2 years have further analyzed the accuracy of RT-CGM. Bode and colleagues[3] found the MM Guardian system to have 67% sensitivity with 90% specificity and 47% false alert for hypoglycemia. A more recent study found MM technology to have a false-positive rate of 16% for mild and 55% for severe sensor hypoglycemia.[4] Large studies performed by the Diabetes Research in Children Network (DirecNet) showed that recent modifications of the MM sensor further improved accuracy and reliability of their RT-CGM device.[5] The DexCom STS system was found to have a Pearson correlation coefficient of 0.88 compared to capillary blood glucose values.[6] Accuracy of the Navigator varied for different glucose ranges (hypoglycemia 73.5%, hyperglycemia 95.4%, and euglycemia 99%).[1] Studies have found both the Guardian and the DexCom systems to be accurate and to significantly decrease hypoglycemia in comparison to controls.[3,6] Maia and associates[7] demonstrated the high accuracy of glucose sensors in children, similar to previous reports.

Indications

One of the motivating reasons for developing continuous glucose monitoring is to detect nocturnal and unrecognized hypoglycemia. Individuals with diabetes become unable to detect signs and symptoms of hypoglycemia with increasing duration of disease[8] and may develop hypoglycemia unawareness by loss of the counterregulatory hormonal response.[9,10] Because the sympathoadrenal response is less pronounced during sleep, it is anticipated that hypoglycemia is more severe and prolonged at night.[11] Hypoglycemia unawareness can be reversed by detecting and preventing hypoglycemic episodes for several weeks.[11,12] RT-CGM helps detect and minimize hypoglycemic episodes.[7,13–15]

Glycemic variability is considered by some to be a more sensitive factor for the development of diabetes-related complications than hemoglobin A1c (HbA1c) alone.[16–19] Ceriello and colleagues[20,21] suggested that postprandial hyperglycemic excursions may be the only independent risk factor of diabetes complications. However, multiple blood glucose (BG) measurements per day are required to establish glycemic variability to achieve optimal diabetes control using conventional glucometers.[22] This can be inconvenient and time-consuming because it is not feasible to perform frequent (>4) glucose monitoring daily.[14] In one DirecNet study, most subjects failed to accomplish frequent (≥6) point monitoring even for a short time, supporting the use and benefits of RT-CGM. In this study, 97% of the subjects completed three-point calibration in ≥40 hours while on RT-CGM, whereas only 19% were able to check their BG ≥7 times per day for 3 days using a home blood glucose meter. BG monitoring <7 times per day is not sufficient to measure hyperglycemic excursions.[23] Glucose sensors are more reliable in detecting glycemic variability and hyperglycemic excursions and are a convenient way to monitor and improve these challenges.[23,24]

Several studies have concentrated on the use of RT-CGM to improve metabolic control to prevent or delay diabetes-related complications. It has been shown that improvement of metabolic control can prevent and/or delay the onset of diabetes complications.[25–27] Hoey and colleagues[28] showed that an improvement in HbA1c was associated with a better quality of life and lower impact of disease burden in children and adolescents with diabetes.

Benefits

Self-blood glucose monitoring (SBGM) via conventional finger stick has been the single most important tool in guiding insulin therapy.[29] There are several issues surrounding capillary BG monitoring that make it inconvenient for patients. These include pain, the time it takes, and the unwanted attention the individual may get from others while checking their BG. RT-CGM can be more discrete than traditional SBGM. The wireless RT-CGM receiver can be kept within 5 feet from the body, thus making it more convenient. RT-CGM requires fewer finger sticks per day to capture glycemic variability. Furthermore, it is a safe, relatively accurate, and easy-to-use system.

Compared to SBGM, RT-CGM shows blood glucose fluctuations in a real-time format, allowing one to see BG fluctuations. Newer models, such as the MM Guardian, are also equipped with predictive alarms to let the user know if they are going to be outside of their target range in a designated amount of time or if the BG is changing too rapidly.

The issue of pain caused by conventional capillary SBGM is believed to be one of the explanations of poor adherence to diabetes self-care.[30] As mentioned earlier, multiple daily BG measurements are required to achieve optimal diabetes control. Very few patients are able to check their BG at least four to five times a day.[22] One of the important benefits of RT-CGM is that it can significantly decrease the amount of finger pricking required for SBGM. While no manufacturer advocates relying or acting on RT-CGM glucose values without confirmation by finger stick, the trending information it provides allows for better metabolic control with potentially fewer BG measurements.

Use of RT-CGM showed an improvement in glycemic control in motivated children and adolescents, as well as in patients with poorly controlled type 1 diabetes without an increase in the number of hypoglycemic episodes.[7,31,32] In addition, as mentioned earlier, studies evaluating the efficacy in determining glycemic excursions found CGM to be a very good method of glucose monitoring and improved glycemic control.[13,32–35]

Studies have indicated that using CGM is beneficial in detecting nocturnal hypoglycemia. Over 65% of children and adolescents experience asymptomatic hypoglycemia regardless of the form of insulin therapy [multiple daily injections or continuous subcutaneous insulin infusion (insulin pump therapy)].[36] The majority of the studies found that CGM was better in determining asymptomatic hypoglycemia than SBGM.[7,13–15] Furthermore, CGM-guided therapy can reduce the incidence and duration of hypoglycemia.[36,37]

Continuous glucose monitoring can provide patients and their providers with information about "hidden problems."[36] Two of the most discussed problems are glucose variability and glycemic response to different foods. RT-CGM makes these problems visible, allowing insulin doses to be adjusted to optimize diabetes control.

Predictive alarms on some systems let the patients know if they are going to be outside of their target range in a designated amount of time. For example, if the BG is changing so rapidly that they will be outside of their target range in 30 minutes, it will alert them so that they can intervene before more serious sequelae ensue.

Ludvigsson and Hanas[14] reported that CGM is an important tool in treating diabetes because it not only improves metabolic control, but also brings new insights, increases motivation, and facilitates treatment. Similar data were shown in a DirecNet study where both pediatric patients and their parents felt that using a RT-CGM system improved their insulin dose adjustments and diabetes management decisions.[15]

Limitations

Lag Time

Glucose sensors detect glucose levels in the IF as opposed to using a capillary blood sample.[38] Early CGM had a lag time of approximately 20 minutes with changes in BG preceding changes in IF, irrespective of whether the BG was rising or falling.[39,40] The delay in the equilibration of interstitial glucose levels may cause a delay in recognizing hypoglycemia and in recovery from hypo- and hyperglycemia. Studies have found a 4- to 10-minute average difference between the BG and the IF glucose, which is ascribed to the difference between individual sensor electrodes rather than the difference between the BG and the IF.[24] MM states that with their current system, IF glucose may lag 4 minutes and the sensor reading may lag up to 10 minutes behind the BG during rapid glycemic changes (data available upon request). However, the same RT-CGM may either trail or lead BGs when the glucose is falling. In only 25% of cases a drop in interstitial glucose preceded the fall in BG.[24] There is currently controversy surrounding the delay in the recognition of and recovery from hypoglycemia. One study indicated no delay in recognizing hypoglycemia but found a prolonged (26 minutes) recovery period.[41] Another study did not find delayed recovery from hypoglycemia[42] and yet another one found good detection of falling BG with mild overestimation of hypoglycemia.[43]

Calibration

Currently available RT-CGM systems need to be calibrated by SBGM an average of one to three times a day to ensure correct reading. RT-CGM is not yet accurate enough to replace SBGM.

False Hypoglycemia

The major limitation of RT-CGM is overestimation of hypoglycemia with a high false alert rate.[44] Several

studies reported a higher degree of inaccuracy with an efficacy of 62.5% in the hypoglycemia range compared to the euglycemic and hyperglycemic ranges and a low sensitivity for hypoglycemia.[13,33,45] This is especially true of the older versions of the sensor electrodes.

Adverse Events

Several studies have found CGM to be safe for all ages.[46,47] Frequently reported problems were discomfort (11.4 %)[13] and skin irritation/pruritis (29%).[48] No trauma, infection, or bleeding was reported with short-term sensor use (≤72 hours).[5,7,46] Interruption in signal between the sensor electrode and the receiver was reported in 12.5–18.5% of subjects.[7,46]

Other Issues

Some clinicians have found that while HbA1c improves after 3 months of sensor use, this decrease in HbA1c is generally not maintained over time. However, the degree of glycemic variability was not assessed. It is speculated that although the HbA1c may return to baseline values, glycemic variability is reduced.

Clinical Applications

If diabetes providers do not believe RT-CGM is beneficial, it will come through in their interactions with their patients. As putting a patient on an insulin pump is only as good as the support and education provided, putting a patient on a RT-CGM system only provides clinical utility if the patient and their family are taught how to put it to best use.

When presenting RT-CGM to patients, its clinical utility and benefits must be discussed. Many patients are hesitant to use it because it means having the transmitter attached to them at all times, and for patients who are on insulin pumps, it means having a second site on their body that they need to worry about. This issue may seem relatively minor to providers, but it can be a significant concern for patients. To help overcome this and other issues, it is more effective if RT-CGM is explained to the potential user as "you need this because…" rather than "this is available…"

Realistic expectations of RT-CGM should be given. Many individuals believe that using RT-CGM eliminates the need for checking BG values. This is not the case. Capillary BG should be checked a minimum of two times per day to calibrate the RT-CGM unit and also to confirm high and low glucose values when the RT-CGM device indicates that the glucose is out of range. RT-CGM is not 100% accurate.[1,3–7] Nevertheless, it still gives good trending information and a good sense of an individual's BG levels most of the time. It puts many families' minds at ease by relieving the fear of hypoglycemia and helps improve metabolic control by targeting postprandial hyperglycemia.

Not all health insurance firms have adopted RT-CGM. With the advent of A codes to better describe what is being prescribed (sensors A9276 per day, transmitter A9277, receiver A9278; **Table 1**) instead of using the miscellaneous E code (E1399), more insurance firms are putting policies in place to approve RT-CGM. However, some are still denying it and the decision must be appealed.

Table 1.
Codes Used When Prescribing a RT-CGM Device

Code	Description
A9276	Sensors, per day
A9277	Transmitter
A9278	Receiver

Note: The miscellaneous code E1399 should no longer be used when prescribing a glucose sensor.

Initial letters of medical necessity (LMN) sent to the insurance company requesting approval for RT-CGM must be strong, direct, and assertive. They should target the clinical problem(s), whether it be elevated HbA1c values, which have the potential for causing costly diabetes-related complications, the presence of complications, fear of hypoglycemia preventing a decrease in HbA1c, extreme glycemic variability, which in turn leads to diabetes complications,[16–19] detection of frequent/masked hypoglycemia, or pregnancy. Both the Diabetes Control and Complications Trial (DCCT)[25,26,30] and the Epidemiology of Diabetes Interventions and Complications (EDIC)[30] studies can be used as supporting documentation. The DCCT was the first study to definitively show the association between good glycemic control and the reduction in the incidence and progression of diabetes-related complications. Furthermore, even if target HbA1c values could not be obtained, researchers found that a reduction in HbA1c was associated with a reduction in the incidence and progression of complications.[25] The EDIC study found that good control earlier in the course of the disease has better long-term outcomes than achieving good control later in the course of the disease, even if the good control achieved early on cannot be maintained over time.[30] Many of the articles referenced previously can also be used as supporting documentation for the necessity of providing insurance coverage for RT-CGM.

Some insurance companies will deny coverage of RT-CGM because they state it is an investigational device. RT-CGM is not an investigational device. It has been approved for patients 7 years and older. For patients <7 years old, a strong LMN stating why RT-CGM would benefit that particular child is necessary.

In order to get the many LMNs written for all of the patients who would like and/or would benefit from RT-CGM, it tends to work easiest if a few hours are set aside every 2 weeks or so during which a batch of letters can be written. Devising a strong template for the LMN that can be tailored to fit each individual's needs will cut down on the time spent writing letters. Batching patients by their health insurance provider also facilitates the writing of the LMN, as different insurance providers may require different information on each patient. However, the basic information required is the same for all individuals. Appeal letters are best drafted from scratch, as they must address the specific reason(s) why RT-CGM was denied.

Once the patient has received their RT-CGM, they are ready to be trained! Training can be done in a variety of ways, including as a scheduled office visit or by the company trainer. When scheduled as an office visit, the Current Procedural Terminology (CPT) codes 95250 and 95251 can and should be used (**Table 2**). At least one company will reimburse individually certified trainers for RT-CGM trainings. Trainers who train under center contracts cannot be reimbursed for RT-CGM trainings because CPT codes exist for this service.

Teaching RT-CGM to a patient and their family is a little abstract initially, because it is difficult to demonstrate all of the components and discuss everything the patient and their family may see on the transmitter before the RT-CGM unit is active. For example, the MM system should not be calibrated if there are trend arrows present on the screen. Also, the sensor status screen will give information including when the next calibration is due and battery status. However, it is impossible to view such data in either of these fields before the sensor is functional. In such cases, the literature and pictures that accompany the RT-CGM system can be used to facilitate the training. It is unreasonable to keep the patient in the office until such data can be viewed, as this would take a minimum of 2 hours once the sensor is inserted and the calibration process started.

As discussed at the Diabetes Technology Meeting in Orlando, Florida, in April 2008, some diabetes clinicians recommend starting slowly with RT-CGM. Different features of the RT-CGM should be activated at different times so as not to overwhelm the family by giving too much information at once (**Table 3**). These clinicians have found that families who are given too much information at once become overwhelmed and stop using the RT-CGM. BG target ranges can be set at the first visit. The DexCom7 STS system has a default target range of 80–200 mg/dl that can be customized by the trainer using computer software; the MM Guardian or MiniLink systems can be customized on the unit itself by the individual. The target alarms can be turned off initially if so desired. The DexCom system will still alert the user if the glucose value drops below 55 mg/dl; that cannot be turned off. When setting target ranges on the RT-CGM for the individual patient, keep in mind how their BG has been running over the past several weeks and if there are other issues that need to be considered.

Table 2.
RT-CGM Billing Codes[49]

CPT code	Description
95250	Ambulatory CGM of interstitial tissue fluid via a subcutaneous sensor for up to 72 hours: sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251	Physician interpretation of CGM report

Table 3.
RT-CGM: Training the Patient

First visit
• Teach the patient about all of the pieces of the RT-CGM device and their function (sensor electrode, transmitter, receiver)
• Discuss sensor calibration, on-screen sensor data, and troubleshooting
• Discuss company's 24-hour help line, where the phone number is located, and when it should be used
• Set BG target ranges
• Have patient insert sensor electrode and start calibration process
• Encourage patient to call their diabetes providers with questions and problems during the next few days
Ensuing visits
• Turn on BG target alarms (this can also be done at the first visit, if desired)
• Set predictive alarms (where available)
• Set rate of glucose change alarms (where available)
Note: These features can be turned on at the first glucose sensor training visit if desired. However, it is recommended to turn them on after the patient has become more comfortable with RT-CGM to prevent the patient from becoming overwhelmed by having too much information and too many alarms ringing all at once.

Our team uses a default target BG range of 80–200 mg/dl; however, if the patient has been having significant hyperglycemia, the upper limit of the target range may be set higher to minimize annoyances from frequent alarms. The upper limit of the target range is then decreased as metabolic control improves.

Various alarms available on RT-CGM include hyperglycemia, hypoglycemia, predictive alarms for sugars that will be below the target range in a certain amount of time, rapidly changing glucose levels, calibration due, and weak/lost signal. While these can all be set up during the initial visit, it is recommended to add the various alarms slowly over the first several weeks of RT-CGM use so that the patient becomes accustomed to using RT-CGM without being overwhelmed by a cacophony of sounds. Encourage patients to call their diabetes providers during the first few days after starting RT-CGM to help them troubleshoot issues that may arise. They should be informed of the company's 24-hour help line.

If the patient is new to insulin pump therapy and has received RT-CGM at the same time, it is recommended to give them time to acclimate to insulin pump therapy before starting RT-CGM. It generally takes about 1 month to become comfortable with insulin pump therapy.

Some patients/families stop using RT-CGM because of frustration with the device or with the accuracy of data. If there are problems with the sensor electrode and transmitter staying attached to the patient, IV Prep ("sticky alcohol") adhesive wipes or extra tape, such as IV3000, Tegaderm, or medical tape, can be used to reinforce adhesion. Additionally, antiperspirant can be used prior to electrode insertion to minimize sweating in that area. Alternate sites for the sensor electrode and transmitter should also be suggested (abdomen, hips, arms, thighs). Skin irritation can be minimized by placing a piece of IV3000 or Tegaderm tape on the skin and inserting the sensor electrode through it. To troubleshoot calibration difficulties and sensor inaccuracy, first make sure that the patient is not calibrating the RT-CGM device during times of rapid glycemic fluctuation, such as when the BG is dropping rapidly or shortly after eating a meal, or calibrating the unit too frequently (more than three to four times per day). The company's customer support line can also be called to help with calibration difficulties. Patients can be quick to stop using new technology that appears to not be working as expected. They should be encouraged to use at least two different sensor electrodes before giving up on their RT-CGM device.

The two RT-CGM units that are currently available commercially, the DexCom7 STS and the MM Guardian/MiniLink, can be downloaded into their respective computer software. Ideally, patients who use RT-CGM will have their receivers downloaded at every diabetes office visit so that the results can be discussed with their diabetes provider. Patients should be encouraged to make use of the option to download their RT-CGM receivers at home for review by themselves and their providers. Depending on the computer used, both companies allow the files to be saved in Microsoft Word or PDF format so that they can be printed or emailed easily. The FreeStyle Navigator has been FDA approved and is the third RT-CGM device on the U.S. market. More information regarding this device was not available at the time this article was written.

In conclusion, RT-CGM is a safe, relatively accurate, easy-to-use device with the potential to improve glycemic control and decrease glycemic variability and incidence of hypoglycemia. Frequent analysis of RT-CGM data helps to make appropriate insulin adjustments, which in turn can reduce the incidence and progression of both short- and long-term diabetes complications. It should be more widely utilized.

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