Journal of Diabetes Science and Technology
Volume 2, Issue 2, March 2008
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MEETING PROCEEDINGS

Clinical Overview of Continuous Glucose Monitoring

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Abstract

Continuous glucose monitoring (CGM) is now available from several companies in the United States for purchase or research studies. This article provides an overview of these devices and reviews the use of sensors for managing diabetes in "real time," as well as the use of retrospective analysis of CGM results.

J Diabetes Sci Technol 2008;2(2):300-306

Introduction

This article contains an overview of continuous glucose monitoring (CGM) in general and covers basic concepts focusing on how to use this technology in everyday clinical practice. There are two major ways people use these devices. Patients use real-time CGM (RT-CGM) throughout the day, looking at their glucose trends and making adjustments in real time to their diabetes management, and they use the alarms to alert them during the day and night of possible hypoglycemic and hyperglycemic events. A second way to look at CGM data is in the retrospective analysis of CGM reports; this information is beneficial to the patient but also has great potential benefit to the health care provider when making treatment recommendations.

One of the main contributions of CGM is to reveal glucose excursions, including lows during sleep and numerous postprandial highs that would be missed by finger stick blood glucose monitoring. In a Diabetes Research in Children Network (DirecNet) study comparing CGM with eight-point testing, the postprandial glucose peaks were two to three times higher using CGM data compared to eight-point glucose testing using a glucose meter.[1] A second important reason for using CGM is for the detection and possible prevention of hypoglycemia. Seventy-five percent of hypoglycemic seizures occur at night,[2] which is of great concern to many patients and parents of children with diabetes. By measuring interstitial glucose levels overnight,

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Abbreviations: (AUC) area under the curve, (CGM) continuous glucose monitoring, (CGMS) continuous glucose monitoring system, (CHO) carbohydrate, (DirecNet) Diabetes Research in Children Network, (HbA1c) hemoglobin A1c, (JDRF) Juvenile Diabetes Research Foundation, (MARD) median absolute relative difference, (RT-CGM) real-time CGM

Keyword: continuous glucose monitoring

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DEXCOM
EXHIBIT 1040

CGM is able to provide an alarm system to alert the patient of pending or actual hypoglycemia. Since 2002 we have been one of five centers participating in DirecNet, a National Institutes of Health-funded study group to assess continuous glucose monitoring in children. From analysis of DirecNet CGM outpatient data, there is about a 25% incidence of nocturnal hypoglycemia, a much higher incidence than commonly detected by discrete home glucose monitoring.

For appropriate and accurate interpretation of CGM data, it is important to understand the physiological background of the CGM measurement. All currently available CGM systems measure interstitial glucose levels and do not measure capillary (blood) glucose levels. The blood and interstitium represent two different physiologic compartments, and there is a physiologic lag between interstitial and blood glucose levels, particularly when glucose levels are changing rapidly. With rapid glucose changes (>2 mg/dl-min) the average lag time is about 18 minutes with about 6 to 8 minutes due to physiologic delay and about 12 minutes due to filters imposed by the sensor algorithms.[3,4] The temporal glucose changes observed in interstitial tissue, however, correlate better with the time course of glucose changes in the brain as compared to the time course of changes in the blood.[5] The lag time between interstitial and blood glucose levels occurs with all the current subcutaneous sensors and has several important clinical ramifications: (1) when the glucose is decreasing rapidly, the alarm for hypoglycemia will be delayed; (2) recovery from hypoglycemia may not be apparent on the sensor and should always be confirmed by a capillary glucose level to avoid overtreatment of hypoglycemia; and (3) calibration of the sensor should not be performed when glucose levels are changing rapidly. When blood glucose levels are stable, there is little difference between interstitial and blood glucose readings, making this a good time to calibrate a CGM system.

Continuous glucose monitoring measurements are not as accurate as discrete glucose measurements. In a DirecNet study to assess the accuracy of the Ultra and FreeStyle home glucose meters, the median absolute relative difference (MARD) when compared to a laboratory reference glucose was about 5%.[6] In DirecNet studies to assess the accuracy of the MiniMed Guardian® and FreeStyle Navigator® CGM systems, their MARD was about 12%.[7,8] A single glucose value can be compared to a digital photograph with many pixels and a continuous glucose sensor to a digital camcorder, where there is lower resolution per frame, but the direction of glucose trends is observed, which allows for prospective interventions.

There are currently four devices used for continuous glucose monitoring: (1) the Paradigm 722 system, (2) the Guardian® REAL-Time system, (3) the DexCom 7-day sensor, and (4) the Navigator (not yet approved by the Food and Drug Administration). An overview of some of the features in each system is presented in **Figure 1**. The first two systems by Medtronic MiniMed now use a small lightweight transmitting device called a MiniLink™ transmitter. The previous MiniMed transmitter was heavier and required strong adhesive tape to secure it onto the skin, which resulted in skin irritation that we are no longer seeing with the MiniLink transmitter. For patients wearing a MiniMed pump, the 722 system allows integration of the pump and the sensor receiver into one device, but the sensor does not currently regulate insulin delivery. The system is calibrated by an electronic transmission of a glucose value from a BD Logic® meter (in the future this will be done using an Ultra meter) or by manual entry of a glucose value from any home glucose meter.

The DexCom system has one of the smallest transmitters and uses the smallest insertion needle (26 gauge). It is the only sensor approved for 7 days of wear. It is calibrated by a cable connection to an Ultra blood glucose meter. The receiver is a separate device, which is worn on the belt.

The Navigator system consists of a sensor, an inserting device, a transmitter, and a receiver. The system is calibrated by a FreeStyle meter, which is built into the receiver.

All the CGM systems have a programmable threshold alarm for low and high glucose levels and an ability to download data. The MiniMed and Navigator systems provide rate-of-change arrows to indicate if the rate of

Device Features

	Paradigm 722	DexCom	Navigator
Rate of change arrows	Yes	No	Yes
Programmable threshold alarm	Yes	Yes	Yes
Projected low alarm	Yes	No	Yes
Days of wear	3	7	5
Ability to download	Yes	Yes	Yes
Ability to integrate with pump	Yes	No	No

Figure 1. Overview of some of the features in each RT-CGM system.

glucose change is >1 or >2 mg/dl -min. The MiniMed Guardian and the Navigator also have a projected low alarm feature. The MiniMed Guardian REAL-Time has predicted low alarms that are based on a projected glucose 5, 10, 15, 20, 25, or 30 minutes into the future, and the Navigator has 10, 20, and 30 minute projected alarms. The DexCom does not have a projected alarm feature at this time. Projected alarms allow the patient to treat pending hypoglycemia before it occurs. In our DirecNet studies we have generally recommended treating a predicted alarm with 10 grams of carbohydrate (CHO) instead of the 15 grams used to treat confirmed hypoglycemia. The predicted alarm also increases the frequency at which hypoglycemia is detected. In a DirecNet study, the hypoglycemic alarm detected 23% of nocturnal hypoglycemic events, but when the hypoglycemia prediction alarm was added, 77% of the hypoglycemic events were detected.[9] Use of a predictive alarm, however, also increases the incidence of false-positive alarms, and in the DirecNet study the false-positive alarm rate increased from 16 to 62%.

Another use of glucose trend information is in the modification of insulin doses. In a DirecNet study using the Navigator, subjects were requested to modify their insulin doses by 10 to 20% based on the glucose rate of change.[10] If the glucose rate of change was between 1 and 2 mg/dl-min, they made a 10% change to their insulin dose, and if the glucose rate of change was >2 mg/dl-min, they made a 20% change to their insulin dose. Subjects found these guidelines helpful and used them in their diabetes management.

The alarm features vary among devices. The Paradigm can be programmed to either a vibrational or an audible alarm; if it is in the vibrational mode and the subject does not respond the alarm will become audible. The DexCom has a strong vibrational alarm that also becomes audible if the subject does not respond. The Navigator has either a vibrational or an audible alarm. None of the CGM devices allow for the alarm type and the alarm thresholds to have separate settings during the daytime and nighttime. Most importantly, none of the CGM devices have a remote alarm. This technology would allow for a bedside device to switch on a light or a stereo system or to relay the information to the parent's bedroom. This is particularly important when a patient sleeps through alarms. In a study of GlucoWatch® alarms, subjects awoke to 40% of the first alarm during the night, but to only 28% of subsequent alarms. The encouraging information from this study was that there were 11 hypoglycemic events (glucose confirmed ≤ 70 mg/dl), and with each event the subject awoke to the alarm, indicating that hypoglycemia per se does not prevent awaking to an alarm.[11] The ability to hear an alarm is partly dependent on where the device receiver is located. The Navigator and DexCom receivers can be placed on a bedside table and will not be buried under blankets, whereas the MiniMed receiver is also the subject's insulin infusion pump, so it may be buried under bedding at night, which muffles alarms.

It is important to individualize the hypoglycemic and hyperglycemic alarm thresholds. If the hypoglycemic alarm threshold is set too high or the hyperglycemic threshold is set too low there will be many false alarms. To provide a framework for the potential number of alarms based on glucose thresholds, it is important to know the amount of time subjects could potentially be above or below different alarm thresholds. In a DirecNet study in children with a mean hemoglobin A1c (HbA1c) of 6.8% after 3 months of Navigator wear, they were above 180 mg/dl about 9 hours a day, above 200 mg/dl for 7 hours a day, and above 250 mg/dl for 3 hours a day.[12] We therefore initially set the high alarm around 240 mg/dl and as their blood glucose levels improve, the alarm threshold can be lowered. In this study, children were less than 70 mg/dl for more than 1 hour each day, less than 60 mg/dl for 30 minutes each day, and less than 50 mg/dl for about 15 minutes each day.[12] We generally set the hypoglycemic alarm to 70 mg/dl each day, but this needs to be modified if the patient has hypoglycemic unawareness, which may require a higher hypoglycemic alarm threshold. The MiniMed Paradigm K pump for pediatrics has a fixed hypoglycemic alarm threshold of 90 mg/dl. In a DirecNet analysis of hypoglycemic alarm settings, an alarm setting of 100 mg/dl would capture 100% of values less than 60 mg/dl; however, there would be a 75% false alarm rate, which is probably unacceptable to most people. Based on these data, I would only recommend a CGM with the ability to modify the hypoglycemic alarm threshold to the individual needs of the pediatric patient.

Because there is sometimes up to an 18-minute lag before a CGM sensor would alarm for hypoglycemia after the blood glucose has become low, some patients have raised concerns that they could have a severe hypoglycemic event (seizure or loss of consciousness) due to this lag time. I have found three CGM records of children having a nocturnal seizure while wearing a CGM. In each case the CGM glucose level was low for 2.5 to 4 hours before the seizure occurred. Two of these episodes occurred when the children were wearing a retrospective CGM monitor,

where glucose levels were not available in real time and there were no active hypoglycemic alarms. In the third case the adolescent was wearing a real-time sensor, which alarmed for 2.5 hours before the seizure, but she was sleeping on her sensor receiver, which muffled the alarms and when her parents entered her room they did not hear the alarms until they removed her bedcovers. To increase the probability of an alarm being heard, parents have been known to put the receivers in a glass or on a brass plate so that the vibrations will be amplified at night.

The ability to use direction and rate-of-change data to prevent the glucose level from rising above or dropping below the target range is an advantage not previously available with traditional blood glucose meters. It is often difficult to predict how a certain food, stress, or exercise might affect the blood glucose. We have found that black coffee in the morning (without added sugar) raises the blood glucose and requires a small bolus of insulin. We had a patient who was using a power drill and the drill slipped and drilled a hole through her thumb. She was wearing a RT-CGM and noticed that her glucose levels were actually decreasing following this event when she was feeling nauseated, so she temporarily suspended her insulin delivery and maintained glucose levels between 80 and 120 mg/dl. Without the real-time glucose and trend information, she would not have suspended her insulin delivery and would probably have become hypoglycemic. Another confirmation of the usefulness of RT-CGM comes from a study using a Navigator in the Race Across America, a marathon bicycle race across the USA.[13] These elite cyclists with diabetes initially wore the Navigator blinded during their training, during which time there was a 5.5% incidence of hypoglycemia. When they wore the Navigator unblinded in training, the incidence of hypoglycemia decreased to 3.7%; and during the race, the incidence of hypoglycemia was 2.7%. Using RT-CGM they were able to decrease their frequency of hypoglycemia, despite increasing the intensity of their physical activity.

Retrospective analysis of uploaded RT-CGM data allows the patient to recognize glucose trends, to make changes to basal rates, carbohydrate-to-insulin ratios, and insulin sensitivity for correction dose, and to modify their food choices and responses to activity. Retrospective analysis of downloaded data is the primary tool the health care provider has in making recommendations to the patient wearing a RT-CGM. The provider must be familiar with the different reports provided by each RT-CGM system. Currently the 7-day DexCom reports provide a trend graph and statistics on glucose levels divided by time blocks. An example of a trend graph is given in **Figure 2**. The MiniMed and Navigator software also provide a sensor modal day, where the glucose patterns over multiple days are plotted by time of day. Examples of Navigator modal days are provided in **Figure 3**, and a MiniMed modal day is provided in **Figure 4**. Because the MiniMed CareLink™ software is integrated with

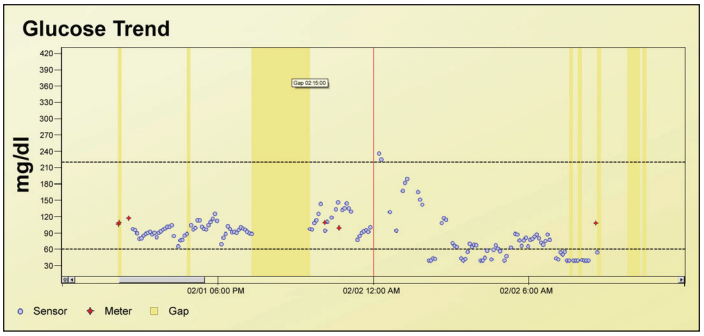

Figure 2. DexCom trend graph.

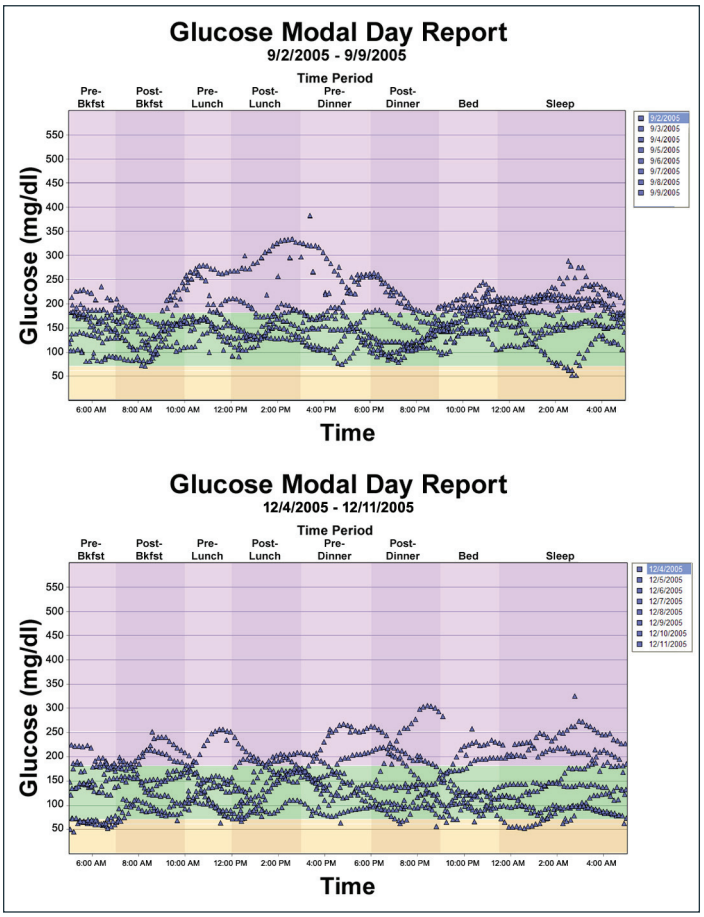

Figure 3. Example of Navigator modal day graphs. **(Top)** First week of data where the mother is responsible for the diabetes management of her 15-year-old son and his HbA1c is 7.1%. **(Bottom)** On the 12th week of the study, the adolescent has now assumed control of his diabetes and his HbA1c is 5.7%.

insulin pump data, it is possible to graph meal-related data based on when the insulin bolus was given for the meal. An example of a sensor meal modal day graph is provided in **Figure 4**. The daily detailed graph allows a detailed picture of eating, insulin doses, and the response to alarms; an example is given in **Figure 5**. All insulin pumps currently provide a "smart pump" feature. If the patient uses this feature for all their meal boluses, it is possible to get an approximate idea of their daily caloric intake, as carbohydrates generally represent about 50% of the calories in their diet. Multiplying their daily total grams of CHO by 8 provides an estimate of their total daily calories. Using this calculation we have found that patients are often underestimating their carbohydrate intake by at least 30%. This underestimation is particularly true if they have missed meal boluses. An example of a missed meal bolus is provided in **Figure 5**.

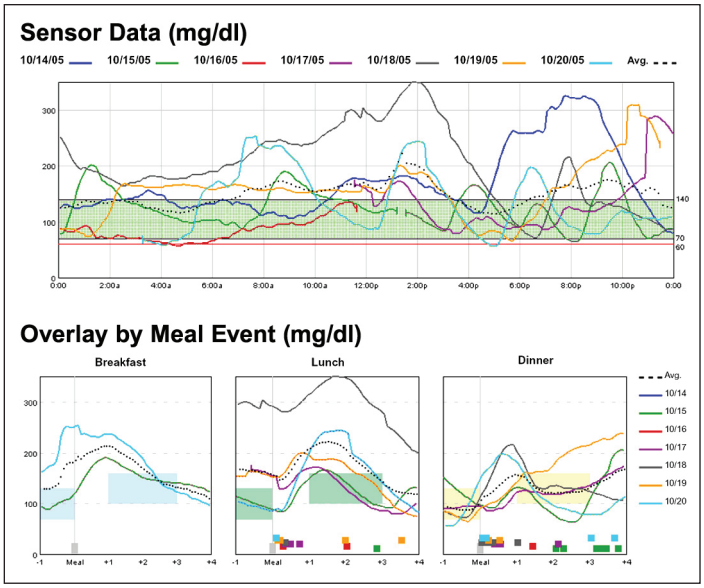

Figure 4. MiniMed sensor modal day and sensor meal modal day reports.

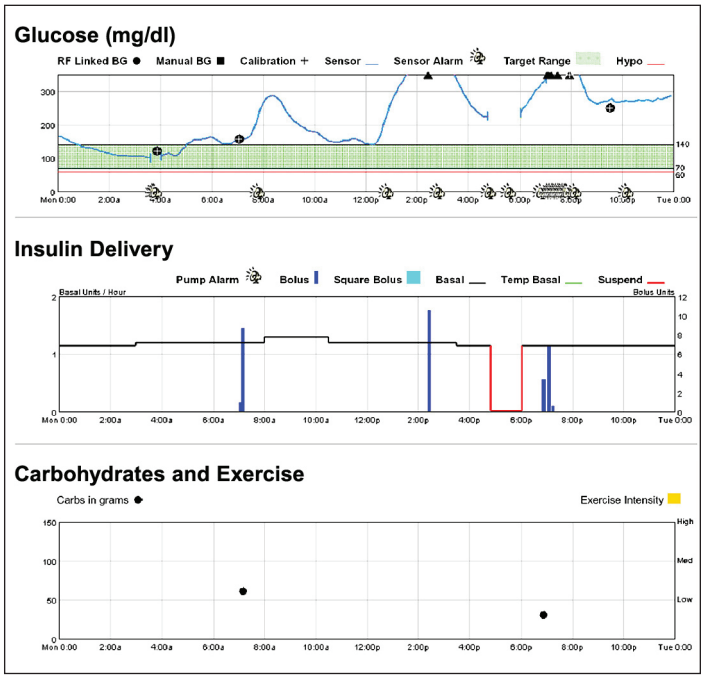

Figure 5. MiniMed daily details. In this graph, several reasons for hypoglycemia are easily apparent: (1) the breakfast dose of insulin was not sufficient for the amount of food eaten (a lower CHO:insulin ratio was needed or CHO were not counted correctly) or the insulin was not given enough time in advance of the meal for the insulin to begin working before food absorption increased the blood glucose; (2) at noon the patient failed to have insulin for the lunch meal (a missed meal bolus); and (3) the subject turned off his insulin pump in the evening when the subject's glucose began to trend downward.

Overview of Studies Using CGMS

A study done by Garg and colleagues[14] using the DexCom sensor evaluated glycemic control when subjects were initially blinded to the RT-CGM readings for 3 days and then the sensors wore worn unblinded for 6 days so the subjects could see their glucose readings. When subjects were able to see and react to their RT-CGM glucose values, they spent 26% more time in the target glucose range (80–140 mg/dl) compared with blinded wear ($P < 0.0001$), and they also spent 21% less time in the hypoglycemic range (<55 mg/dl) and 23% less time in the hyperglycemic range (>240 mg/dl).

Using the MiniMed system, Deiss and colleagues[15] enrolled 162 subjects with HbA1c levels >8.1% in a 3-month trial to assess the impact of RT-CGM on HbA1c levels. Of the three groups, the control arm had a 0.4% decrease in HbA1c at the end of 3 months; the group using the sensor for 3 days every 2 weeks had a 0.7% decrease in HbA1c and the group using the sensor continuously had a decrease in HbA1c of 1%, which was statistically significant when compared to the control group ($P = 0.003$). Continuous use was clearly better than intermittent use.

Medtronic/MiniMed conducted a second study to evaluate the clinical effectiveness and safety of the Paradigm 722 system, a device that combines an insulin pump with real-time CGM, as compared to using an insulin pump with standard blood glucose monitoring.[16] In this seven center, 6-month, randomized, treat-to-target study of 146 subjects, 98 adults and 40 adolescents completed the trial. Subjects had an initial HbA1c of ≥7.5%. HbA1C levels decreased significantly ($P < 0.001$) in both the sensor (–0.7%) and the control group (–0.6%), and between-group differences did not achieve statistical significance. A higher percentage of sensor subjects

reached the predetermined HbAlc target of 7.0% (38% vs 19%, $P = 0.003$). While the control subjects had a significant increase in their hypoglycemia area under the curve (AUC), the sensor subjects did not have an increase in hypoglycemia AUC while simultaneously improving their HbA1c levels. The effect of compliance was significant; each 10% increase in sensor wear was associated with a 41% increase in the probability of a 0.5% reduction in HbA1c. In our adolescent patients at Stanford, there were some subjects who took great advantage of real-time data and made significant improvements in their diabetes control. There were other subjects who did not take advantage of this information and ignored alarms, trend information, and were less compliant in wearing the sensor. Until there is a closed loop, it became very clear that RT-CGM is a behavior modification tool. To gain maximum benefits from the sensor, a patient needs to be willing to modify his/her diabetes behavior. It was concluded that use of the Paradigm 722 system in moderately to poorly controlled type 1 diabetes subjects improves glycemic control compared to baseline without increasing the amount of time spent in the hypoglycemic range. Subjects with greater sensor utilization predicted a greater improvement in HbA1c levels.

DirecNet conducted a feasibility study to assess use of the FreeStyle Navigator RT-CGM ("Navigator") in children with type 1 diabetes. Thirty type 1 children using insulin infusion pumps participated in this 3-month study.[12] Mean hemoglobin HbA1c improved from 7.1% at baseline to 6.8% at 13 weeks ($P < 0.02$), and the percentage of glucose values between 71 and 180 mg/dl increased from 52 to 60% ($P < 0.01$). Subjects and parents reported high satisfaction with the Navigator on the continuous glucose monitor satisfaction scale. There was high compliance with sensor use, averaging 149 hours/week during the first 4 weeks, which decreased slightly to 134 hours/week during the last 4 weeks. The children in the study were involved in a number of different activities, including basketball, volleyball, wrestling, soccer, swimming, and surfing. As part of this pilot trial, subjects were given RT-CGM algorithms designed to provide guidelines for the use of both real-time and retrospective data.[10] A complete copy of the algorithms used in the study is available in the appendix of the original article. An example of one of the algorithms is given in **Figure 6**, which provides guidelines on how to use the rate-of-change arrows. Use of the algorithms increased subjects' autonomy, which is evidenced by the frequency of therapy adjustments made by patients and their families. After 1 week of RT-CGM use, 10% of subjects reported making changes to insulin-to-carbohydrate ratios and 20% made changes in basal rates.[10] This increased to 25% reporting making a change in insulin-to-carbohydrate ratios and 32% adjusting basal rates by the end of the study. The success of these algorithms warrants further study and consideration when teaching patients how to respond to CGM data. Central to these algorithms is a thorough understanding of insulin action profiles. Teaching the onset, peak, and duration of all types of insulin the patient is using is critical. For patients using smart insulin pumps with bolus calculators it is important to review their insulin onboard settings and to encourage the use of this feature to prevent insulin "stacking." Patients using the Navigator system reported that it helped them in adjusting their insulin doses and did not make them think too much about their diabetes. Sixty percent of parents thought the Navigator taught them new things about their child's diabetes that they did not know before, and 93% felt safer wearing the Navigator.

↑ (90° Up) Increase meal dose by 20%
↗ (45° Up) Increase meal dose by 10%
→ (No change) No change in meal dose
↘ (45° Down) Decrease meal dose by 10%
↓ (90° Down) Decrease meal dose by 20%

Figure 6. Guidelines for using Navigator rate-of-change arrows to modify insulin dose adjustments.

In conclusion, it is important for people beginning RT-CGM use to have reasonable expectations and know that there will be lag times and that the sensor will not be as accurate as their home glucose monitor, but that it will allow for trend analysis. There are going to be false-positive and false-negative alarms. Patients will see fluctuations in their glucose levels that they were not aware of previously. They can use sensor trends in making real-time decisions. It has been our experience that patients who have dramatic improvements in their HbA1c are looking at their RT-CGM 10 to 40 times a day. When wearing the pump, we always recommend using a bolus calculator to account for the insulin board and to prevent insulin stacking. To take full advantage of the system, patients should upload and review their results at least weekly.

Real-time CGM is a powerful tool in diabetes management and will be very valuable to anyone wanting to improve their diabetes control. I anticipate that it will take several

large clinical trials [such as the Juvenile Diabetes Research Foundation (JDRF) randomized clinical trial of CGM] demonstrating an improvement in HbA1c levels and/or hypoglycemia risk before RT-CGMS receive routine reimbursement from insurers. Education is critical when using a new technology. To help provide education about the general use of RT-CGM and to provide patients with detailed examples of how to use each device, an online teaching program has been developed by the JDRF randomized clinical trial group and should be available for general use in the next year.

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