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Continuous Glucose Monitoring: Current Use and Future Directions

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Abstract

Continuous Glucose Monitoring (CGM) is an emerging technology that provides a continuous measure of interstitial glucose levels. In addition to providing a more complete pattern of glucose excursions, CGMs utilize real-time alarms for thresholds and predictions of hypo- and hyperglycemia, as well as rate of change alarms for rapid glycemic excursions. CGM users have been able to improve glycemic control without increasing their risk of hypoglycemia. Sensor accuracy, reliability and wearability are important challenges to CGM success and are critical to the development of an artificial pancreas (or closed-loop system).

Keywords

type 1 diabetes; continuous glucose monitoring; closed-loop system; artificial pancreas; nocturnal hypoglycemia

Introduction

This article provides an overview of continuous glucose monitoring, including clinical uses, description of devices, current challenges, advances in the field, and future directions. CGMs are used to provide a more complete picture of blood glucose patterns and trends, both retrospectively through data downloads, and in real-time through receiver displays of glucose levels. Real Time CGMs (RT-CGM) are able to provide an alert to patients during actual or pending glycemic excursions, so that timely treatment can be given. CGMs are

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Daniel DeSalvo declares that he has no conflict of interest.

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particularly helpful in detecting glucose excursions at times that the user does not typically check capillary blood glucose, such as the first few hours following a meal, and overnight-- a particularly vulnerable time for hypoglycemic seizures. [1]

Currently approved CGM devices utilize glucose oxidase-based electrochemical subcutaneous sensors to detect glucose levels in the interstitial fluid. An electric current is generated as the glucose is oxidized by the sensor, and the electric current is then transmitted to the receiver or monitor. The data is filtered to remove sensor “noise” and then a glucose value is provided every 1–5 minutes on the receiver screen, allowing the user to see current glucose levels and trends. [2–4]

Uses

For patients using either insulin pumps or multiple daily injection (MDI) therapy, CGMs can be useful in improving glycemic control without increasing the risk of severe hypoglycemia [5, 6]. In multiple clinical trials, adults with T1DM have shown improved glycemic control (lower HbA1c) using CGM compared to routine self-monitoring of capillary blood glucose [7–9]. Similarly, children who use a CGM on a consistent basis show improved HbA1c levels without an increased frequency of hypoglycemia [10]. The STAR 3 study, which included 485 subjects who switched from MDI and traditional blood glucose testing to CGM augmented insulin pump therapy, showed improved HbA1c without increased rates of severe hypoglycemia or DKA in both adults and children [11].

Because CGMs act in real time, they are able to provide important information and alerts to the user. At the most basic level, CGMs can alert the user of hypo- or hyperglycemia via low and high alarms set to user-defined thresholds. To minimize the frequency of alarms and thereby avoid alarm fatigue, we suggest starting new users on a low glucose alert of about 60 mg/dl and a high sensor alert of about 240 mg/dl. After becoming more comfortable with the CGM, the high and low sensor alerts can be honed-in to a more narrow target range and adjusted based on individual patient safety, tolerance for alerts and for the time of day (using different thresholds during the daytime and nighttime). Although some hypoglycemic episodes will be detected 10–20 minutes late because of sensor lag and sensor inaccuracies, this still provides sufficient time to prevent a severe nocturnal hypoglycemic event such as a seizure. In one report of 5 nocturnal hypoglycemic seizures where subject were wearing CGMs, the sensor detected glucose values <60 mg/dl for 2.25–4 hours before seizure activity, allowing ample time, even with sensor lag, for hypoglycemia to be detected [12].

An additional feature that may be available in CGMs is predictive alerts for hypo- or hyperglycemia. This is an optional alert setting that alarms the user before the sensor glucose reaches the low or high alert threshold. The longer the prediction horizon is set into the future, the more likely an event will be detected early, but there is also a higher likelihood of false alarms. The experienced user can use this data to prevent hypoglycemia. For example, if projected to be hypoglycemic in 20 minutes, we recommended taking 10 grams of carbohydrates to prevent the low.

The rate of rise and fall alert is another optional setting on CGMs. If this option is turned on, the user is alerted when sensor values are rising or falling at a rapid pace. Using this alert requires the user to adapt to having alerts sound when the glucose value is in the normal range. A rapid increase in glucose values will often occur with a missed meal bolus, therefore alerting the user to give the missed insulin dose. In our clinical experience, we have found that a rate of change alarm of 4mg/dl/min will detect many missed meal boluses with a relatively low false alarm rate. RT-CGM systems allow the user to set a different rate of change threshold for rising versus falling glucose values, therefore allowing the user to set a lower rate to falling glucose levels in an effort to mitigate hypoglycemia, while avoiding alarm fatigue for rising glucose values. In future versions of CGMs, it would be useful to provide the option of setting different rate-of-change thresholds for different blood glucose ranges (e.g. 2 mg/dl/min for falling glucose less than 120mg/dl versus 3mg/dl/min for falling glucose in the 120–200mg/dl range, and 4 mg/dl/min for falling glucose greater than 200mg/dl).

New CGM users should be counseled to avoid giving multiple boluses to correct postprandial hyperglycemia which can result in “stacking” of insulin and cause delayed hypoglycemia. Instead, postprandial hyperglycemia can be mitigated by giving the insulin bolus several minutes before the onset of eating. Waiting to eat meals 20 minutes after a bolus of rapid-acting insulin has been shown to result in better postprandial glucose levels and improved glycemic control [13]. In our practice, we suggest waiting 10 minutes before eating if the glucose is 100 mg/dl, and adding 5 minutes for each 50 mg/dl above 100. An additional tool for managing postprandial hyperglycemia is changing the content of the meal by adding more protein and fat to delay gastric emptying.

Use in Hypoglycemic Unawareness

Hypoglycemic unawareness is quite common with about 30% of adults with type 1 diabetes affected [14]. Surprisingly, hypoglycemia unawareness is also common in children regardless of duration of diabetes. In one study [15], 29% of young children 3–8 years old and 29% of adolescents 12–18 years old failed to release adrenaline in response to hypoglycemia. Furthermore, parents who were blinded to their child’s glucose level failed to recognize hypoglycemia 71% of the time. Blunted counterregulatory hormone response is especially prominent during sleep in patients with type 1 diabetes as well as healthy subjects [16]. This highlights the importance of a robust low glucose alert that can effectively awake a hypoglycemic patient, or for remote monitoring where a significant other can respond to the hypoglycemic alarm.

For patients with hypoglycemia unawareness, the low-alarm setting should be set at a higher level. While the higher threshold for a low glucose alert will likely result in more false alarms, the likelihood of missing a severe low is minimized. In a study by Ly, et al.[17], adolescents with type 1 diabetes with hypoglycemic unawareness who demonstrated blunted epinephrine responses on hyperinsulinemic hypoglycemic clamp studies were randomized to either standard glucose monitoring or RT-CGM with a low alarm set to 108 mg/dl (6 mmol/l) for 4 weeks. Repeat hypoglycemic clamp studies demonstrated an improved counterregulatory hormone response for the patients randomized to CGM.

Retrospective use of CGM data

CGMs are equipped with the ability to download data for review of glucose patterns. The historical data helps to inform users and their healthcare team of trends over multiple days. While a conventional blood glucose log or glucometer download provides snapshots of glycemic control, a CGM download shows the complete picture, particularly providing post-prandial glucose levels and overnight glucose values that are often missed with conventional finger-stick testing. This allows the clinician to make important changes to the insulin regimen in an effort to improve control.

A common pattern observed in CGM downloads is overcorrecting low blood glucose with resultant hyperglycemia. This can be avoided by using the 15:15 rule: limiting fast acting carbohydrate intake to 15 grams and waiting 15 minutes to recheck the capillary glucose before taking additional carbohydrates.

Uses of CGM in other populations

CGM use has not been limited to patients with diabetes. For example, CGMs have been utilized in the ICU setting because hyperglycemia during critical illness is associated with adverse outcomes [18]. In the NICE-SUGAR multicenter trial, a blood glucose target of 140–180 mg/dL proved safer than targeting normoglycemia (via intensive blood glucose control with a target of 81–108 mg/dL) [19]. An accurate CGM could be used in ICUs to maintain glucose levels in a safe glucose target for critically ill patients. In one randomized trial the use of real-time CGM significantly decreased the risk of hypoglycemia in ICU patients receiving assisted ventilation [20].

In a recent landmark study, real-time CGM was used in an advisory mode to achieve tight glycemic control with a low incidence of hypoglycemia in 444 infants having cardiorespiratory bypass surgery [21]. Unfortunately in this study the tight glycemic control did not improve their infection rate, mortality, length of stay, or measures of organ failure. It should be noted, however, that the tight glycemic control was only initiated for a relatively short period of time in this young cohort (median of 2 days). Future studies using real-time CGM and full closed-loop control may provide different outcomes, particularly in populations with prolonged periods of hyperglycemia under usual care.

CGMs have been used in newborn infants at risk for neonatal hypoglycemia. In this setting, CGM detects many more hypoglycemic episodes than standard glucose testing [22]. Of note, the severity or duration of hypoglycemia required to cause neuronal injury in a neonate is unknown, so it is unclear what benefit treating hypoglycemia will have in this patient population [23].

Patients with Cystic Fibrosis [13] who are at risk for developing Cystic Fibrosis-Related Diabetes (CFRD) have benefited from CGM use. The diagnosis of CFRD is especially important because introducing insulin can aid in clinical improvement in weight and lung function in CF patients, and CGMs have been more effective than oral glucose tolerance test in revealing altered glucose metabolism in these patients [24].

Finally, CGMs can be an effective tool in monitoring patients with glycogen storage disorders, especially when combined with urine ketone and/or blood lactate measurements [25, 26].

Challenges

Lag Time

One limitation of using interstitial fluid glucose is the lag time between serum glucose levels to interstitial glucose levels. While the physiologic lag from serum glucose to interstitial fluid is estimated to be about 5 minutes [27], the value displayed on the CGM receiver typically lags behind capillary blood glucose by an average of 15 minutes [28], due to the transit time of IF glucose through the sensor membrane (1–2 minutes) and filtering of the signal by the CGM device (3–12 minutes) [29]. The lag time is especially pronounced during rapid glucose changes (>2 mg/dl/min), and may be different during a rise versus fall in blood glucose [30]. The major component contributing to the lag time is the filter imposed by the sensor software because of “noisy” sensors. As sensors become increasingly stable and accurate, less filtering will be required and sensor lag times will be reduced.

Accuracy

Sensor technology has rapidly improved over the last decade and each new generation of sensor has greater accuracy and less lag time. The initial Medtronic real-time sensor had a mean absolute relative difference (MARD) of 19.7% and their current Enlite sensor (Medtronic; North Ryde, Australia) has an MARD of 13.9% [31]. The initial Dexcom sensor (Dexcom, Inc.; San Diego, CA) had a MARD of 26%, and the current Dexcom G4 System has an MARD of 14% [32].

At times sensors perform very well with excellent accuracy, but at other times they can have significant inaccuracies, thereby limiting the use of CGMs in making real time treatment decisions (i.e. insulin dosing). It has been our experience that not all sensors are created equal, even within the same lot number. Some sensors can be amazingly accurate, while others from the same box do not function well.

Current sensors are generally less accurate in the first 6 to 24 hours, probably secondary to local tissue changes following tissue trauma at the time of insertion, and are generally most accurate during the 2nd to 6th day of wear. The initial sensor instability may be due to the insertion wound causing inflammatory changes with neutrophils and eosinophils consuming oxygen and glucose and generating hydrogen peroxide. Nitric oxide [33], mast cells releasing histamine [34], microhemorrhages [35] and cytokines such as interleukin-1 [36] may also have a direct effect on lowering sensor output.

With prolonged wear, collagen formation around the sensor may decrease perfusion and therefore alter sensor performance. Transient decreases in sensor output may occur even when a sensor is otherwise functioning well due to changes in local perfusion due to pressure (i.e. nocturnal sensor attenuation when a patient is lying on their sensor) [37] or due to vasoconstriction [38]. CGM sensors tend to be less accurate during periods of intense fluctuations in blood glucose values, especially at hypoglycemic levels [28]. Inserting into a

lipohypertrophied area may also cause sensor inaccuracy, but this has never been studied. This could be an important issue in many patients given that the favorite sites for insulin administration are often the preferred sites for sensor insertions as well.

To optimize sensor accuracy, the user must calibrate the CGM by entering capillary glucose values, typically twice daily. Calibration is usually not as effective during periods of steep rise or fall in glucose levels, so the best time to calibrate is before meals when glucose levels are most stable [39], however this recommendation may be sensor specific, and depend on the filtering of the sensor signal. It has been reported that the Dexcom sensor can be calibrated with rapidly changing glucose levels [40].

Sensors are calibrated using home glucose meters, and these meters also have inaccuracies. When sensors are calibrated with a laboratory glucose analyzer the MARD can improve by about 8% [40]. Fortunately the accuracy of home glucose meters are showing significant improvements with new meters such as the VerioIQ (LifeScan; Milpitas, CA) and Bayer Contour Next (Bayer HealthCare LLC; Tarrytown, NY) producing about 95% of their readings within $\pm 10\%$ of reference glucose values, as long as the finger is clean before the blood test is taken.

Reliability

The reliability of CGMs to continuously report glucose values remains a critical issue. In devices that display glucose values every 5 minutes, there should be approximately 288 reported values each day after accounting for calibration. In recent studies, 86% percent of Enlite sensors were still functioning at the end of 6 days of wear[31], and 94% of Dexcom G4 sensors were functioning on day 7 [32]. This represents an improvement over previous generations when the Guardian RT provided values 82% of the time and the DexCom STS averaged 73% during routine use [41].

Feasibility/Wearability

An important barrier to effective CGM use, especially in children, is feasibility/wearability. In the Pediatric Onset Study, which examined CGM augmented insulin pump therapy in newly diagnosed patients compared to conventional self-monitoring, the improved glycemic control was lost in children who did not use the device with regularity [42]. Similarly, in the JDRF CGM randomized controlled trial, only 21% percent of children used the device for the full 12 months, and those who used the device less frequently did not show improved glycemic control [7]. Clearly, the wearability or user-friendliness of CGMs needs to be addressed in order for children to fully benefit.

Reasons why CGMs are not used with regularity include pain and discomfort with inserting the sensor, problematic equipment, device inaccuracy, issues with insurance approval, and a general feeling that the device is annoying, a hassle, and interfering with life [43]. Another possible issue with CGM wearability is the size of the device. Development of smaller, implantable devices with ultrafine needles could be more acceptable to the user, resulting in increased use [44]. Implanted sensors could potentially relieve patients of having to wear an external device, with the associated skin reactions, and are currently being tested in pigs with implantation for over one year and calibrations every 10 days [45]. Additional

technologies include implanted fluorescent sensors (Senseonics, Germantown, MD; EASD, 2011). A fluorescent sensor has the advantage of having increased accuracy in the hypoglycemic range. It is possible that future closed-loop systems would utilize two different sensor technologies with complementary regions of accuracy. Noninvasive methods such as Raman spectroscopy and infrared measurements have proven difficult due to considerable problems with noise and specificity.

A final factor affecting feasibility of CGMs is the ability to wear the sensor for a prolonged period of time. Commercially available CGM sensors are approved up to 1 week, but there are many patient reports of extending sensor wear significantly longer by re-taping the sensor site.

Advances in the Field/Future Directions

In the future, the real time CGM data could be transmitted either directly or indirectly to a cell phone. The Diabetes Assistant (DiAs) was developed at the University of Virginia and currently uses a USB cable to connect a Dexcom receiver to a cell phone [46]. Once the data is transmitted to the cloud, remote monitoring protocols can be set up so a parent could be alerted when their child exceeds hyper and hypoglycemic thresholds. This would be particularly important for children sleeping in a separate room, young children attending school, or for an adult with type 1 diabetes traveling and sleeping alone. We have used the DiAs remote monitoring system in a diabetes camp and effectively eliminated nocturnal hypoglycemic events lasting greater than 30 minutes.

A timely and accurate CGM is essential for closed-loop studies. Since the sensor is driving insulin delivery, a sensor that is reading too high can cause over delivery of insulin and resultant hypoglycemia. To decrease the risk of sensor errors causing a severe hypoglycemic event there is a staged approach to implementing sensor-determined insulin delivery with the first stage only allowing the sensor to modify insulin delivery to prevent hypoglycemia; a second stage including a treat-to-range algorithm wherein the sensor only determines insulin delivery for predicted glucose values above or below glucose thresholds that provide a buffer of 60–80 mg/dl for an inaccurate sensor; and the final stage would be a fully closed-loop to a glucose target.

It remains unclear what amount of sensor error is acceptable for closed-loop control. Surprisingly, in simulation studies a calibration error of 40% did not result in severe episodes of nocturnal hypoglycemia [47]. While sensor inaccuracy can result from miscalibration, they can also have random, intermittent periods of time where they become inaccurate, requiring recalibration. It is essential for these episodes to be detected or for sensors to become so reliable that these episodes do not occur. One approach to detect these periodic episodes of sensor inaccuracy is to wear multiple sensors as has been proposed by Castle [48]. Another approach would be to use two sensors using different technologies such as glucose oxidase and fluorescent based sensing.

Conclusion

In their current form, CGMs have proven to be effective tools in improving glycemic control without increasing the risk of hypoglycemia. However, expectations should be tempered as there continue to be issues with sensor accuracy, reliability, wearability, and lag time. Recent advances in CGM technology have been very promising in these areas. CGMs will play an increasingly important role in the future, as diabetes technology continues to improve. The full potential for CGMs has yet to be realized, but going forward, CGMs could be used for remote monitoring via cell phones or the internet in patients with a history of severe hypoglycemia, and for initiating suspension of insulin delivery when there is hypoglycemia risk. Finally, CGM will play a critical role in achieving a fully functional closed-loop system.

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