Mini Review

Continuous glucose monitoring

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ABSTRACT

Continuous glucose monitoring (CGM) technology with its recent development in the real-time feedback has got the potential to revolutionize diabetes care in the near future in the arena of the rapeutic interventions and flexibility in variations in lifestyle or dietary intake. CGM has made the attainment of near-normal blood glucose concentrations, a practical goal for most patients with diabetes.

Key words: Continuous glucose monitoring, real time, flexibility

CGM: A Significant Advancement in Diabetes Care

Intensive control of blood glucose in the diabetes management requires accurate determination of blood glucose concentrations and needs application of state-of-the-art technology. Until very recently, this determination could only be achieved by the attainment of multiple capillary blood glucose determinations each day, a practice that is cumbersome, inconvenient, expensive, and a significant disincentive to achieving target blood glucose goals. Even when applied conscientiously, self-monitoring of blood glucose (SMBG) provides only a snapshot blood glucose concentration without providing any information about the direction or rate of blood glucose change. As a result, many patients are unable to achieve blood glucose targets despite testing their blood glucose multiple times daily. CGM represents a significant advance because it 1) provides real-time information about current blood glucose (or, more accurately, interstitial fluid glucose concentrations), 2) provides short-term feedback about the effectiveness of diabetes interventions (such as insulin administration), and 3) it provides warnings when blood glucose concentrations become dangerously high or low.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.104056

Who will benefit from CGM?

Analyzes from two important trials showed that those subjects who were not committed to wearing the device did not benefit, whereas those who were committed had improvements in the primary outcome. The technology works when it is used. The conclusion is that like CSII therapy, benefit can be predicted by appropriate patient selection.[1,2]

While it is evident that compliance is an important issue, proper patient selection definitely improves the outcome. It is apparent that two types of diabetic individuals will potentially benefit from CGM. First, all type 1 diabetes patients are candidates for CGM, because all patients with type 1 diabetes are prone to large fluctuations in plasma glucose, especially hypoglycemia. These individuals are not able to secrete endogenous insulin and, therefore, cannot suppress the circulating concentration of insulin when their glucose level is dropping to hypoglycemic levels. Second, type 2 diabetic individuals who are dependent on exogenous insulin (which usually occurs after several years of diabetes) may also benefit from CGM. This is particularly true if they experience hypoglycemia when trying to maintain their A1C < 7%. In fact, any individual who experiences hypoglycemia will benefit from the hypoglycemia warning that CGM provides.

Review of the CGM Technology

Our current devices are based on the premise that interstitial fluid glucose is related to blood glucose due to

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diffusion across the capillary wall. CGM systems operate by measuring the glucose levels in interstitial fluid. There are currently 3 systems on the market using two different technologies. Sensor devices developed by Dexcom (San Diego, CA; Dexcom SEVEN) and Medtronic (Paradigm Real-Time and Paradigm Guardian) use a glucose oxidase methodology. The enzyme is embedded onto the sensor so that glucose and water will form gluconic acid and hydrogen peroxide. Under a basal electric current, the hydrogen peroxide dissociates, and a modified charge is produced directly proportional to the concentration of the glucose. The other available method from Abbott Diabetes Care (Alameda, CA), termed "wired enzyme" technology for their sensor (Freestyle Navigator), uses glucose oxidase coupled with osmium-based mediator molecules anchored on a polymeric backbone film.[3]

Currently available CGM devices are considered minimally invasive enzyme-coated electrodes to measure interstitial glucose concentrations and convert these values to blood glucose levels. The information stored in the receiver is then converted into estimated mean values of glucose standardized to capillary blood glucose levels measured during calibration. Using an applicator or self-insertion device, a thin plastic sensor is inserted just under the skin of the abdomen or the upper arm. These devices can display real-time glucose values and glucose trends, and some can also sound an alarm or vibrate when they detect hyperglycemia or hypoglycemia. The receiver can store information for later use, and long-term data can be downloaded to a computer. Devices using enzyme-coated catheters require frequent calibrations to correct variations in the reaction between the electrode and the subcutaneous tissue, as well as fluctuations in glucose and oxygen diffusion at the site of the electrode.

Accuracy and Comparison with Capillary Blood Glucose Meter

CGM systems have the potential to greatly affect the management of diabetes. The accuracy of the currently available devices has been studied by a number of investigators, and many report limited sensitivity, particularly in the detection of hypoglycemia. A variety of methods has been used to evaluate the accuracy of the devices, including relative absolute difference and error grid analysis. Relative absolute difference is calculated by subtracting the reference glucose from that obtained by the device, then dividing this by the reference value and multiplying by 100 to obtain a percentage. The lower the percentage is, the greater the accuracy of the device.

The Diabetes Research in Children Network (DirecNet) is a network of 5 clinical centers whose focus is the use of glucose monitoring technology in children with type 1 diabetes. It has evaluated the accuracy of the Medtronic first- and second-generation CGM systems. Using the relative absolute difference, these and other studies have found that first- and second-generation CGM devices routinely overreported nocturnal hypoglycemia with a high false detection rate. Bode *et al.* compared home blood glucose monitors with the results obtained using Medtronic's MiniMed Guardian and found an absolute relative error of 21.3%, with the sensor reading an average of 12.8 mg/dl lower than the conventional home meter.[4] In this study, the effect of real-time alarms on glucose excursions was also evaluated, with the hyperglycemia alarm able to detect values ≥ 250 mg/dl with a sensitivity of 63%, specificity of 97%, and false alarm rate of 19%. Hypoglycemia alarms detected values of ≤ 70 mg/dl with a sensitivity of 67%, specificity of 90%, and false alarm rate of 47%. Although the sensitivity and specificity are poor, the investigators found that alarms significantly reduced the duration of hypoglycemic excursions. Garg *et al.* evaluated DexCom's CGM 7-day sensor and found a mean relative absolute difference of 13 ± 10% when measured in the hypoglycemic (< 70 mg/dl) range, 20 ± 22% in the euglycemic range, and 33 ± 32% in the hyperglycemic (> 180 mg/dl) range.[5] With the low alert set at 80 mg/dl, hypoglycemia was detected with 88% sensitivity, 91% specificity, and 54% positive predictive value. Using fixed-point Clarke error grid analysis, the investigators found that 97% of values fell in the clinically acceptable zones A and B, as described below.

Some have suggested that the reduced accuracy in the hypoglycemic range, especially at night, may be the result of the lack of constant lag period between interstitial and plasma glucose. If true, this would have implications about the best time to calibrate the monitor. Techniques such as those proposed by Feldman *et al.*, where calibration only occurs during periods of slow glucose change, may help to improve accuracy and reduce the occurrence of false alarms.[6] Evaluating the accuracy of these devices is not simple because most conventional measures of accuracy, such as correlation, regression, or even the original Clarke error grid, compare measurements taken during static points in time and fail to take into account the temporal nature of the values. The continuous glucose error grid appears to be a more appropriate measure of accuracy, but it is time-consuming, and some are concerned that this method may fail to detect differences in accuracy between devices. Although the currently available data suggest limited accuracy of these devices compared to capillary

blood glucose measurement (especially in the hypoglycemic range) and point to the need for improvement in the technology, it is important to remember that both CGM and capillary measurement have limitations and that both provide estimates of plasma glucose concentration as determined by a gold standard assessment.

Hypoglycemia

According to several authors, nocturnal hypoglycemia may account for nearly two-thirds of the justification for prescribing CGM to diabetic patients. Nocturnal hypoglycemia is often asymptomatic, even in those with normal glucose awareness while awake. This can be particularly important in children, in whom the literature suggests 30% of CGM recordings revealed nocturnal hypoglycemia < 40 mg/dl.[7]

Hyperglycemia

In many diabetic patients, daytime hyperglycemia may be easily overlooked. This may either be a result of insufficient adherence to blood glucose self-monitoring or monitoring practices that do not cover the entire day. CGM can be particularly useful in detecting postprandial hyperglycemia. Diabetic patients are typically trained to monitor blood glucose before meals and at bedtime, but rarely several hours after a meal. CGM may also help detect nocturnal hyperglycemia and those with the dawn phenomenon or Somogyi effect. The dawn phenomenon describes early morning hyperglycemia as a result of growth hormone release in early morning hours, whereas the Somogyi effect describes fasting hyperglycemia as a result of the counter-regulatory hormone response to hypoglycemia in the middle of the night.[8]

Efficacy

A pediatric study by the Direct Net Study Group demonstrated a reduction in A1C from 7.1 ± 0.6% to 6.8 ± 0.7% (P = 0.02) among 30 type 1 diabetic adolescents who used the Navigator CGM system for 13 weeks after a 1-week period of blinded use.[9] Another study by the same group compared use of the MiniMed CGM system with an 8-point capillary blood glucose determination profile over 3 days among a group of 200 children with type 1 diabetes.[10] Apart from demonstrating that only 10% of patients complied with the rigorous 8-point capillary testing protocol, this study demonstrated that CGM tended to overestimate the occurrence of overnight hypoglycemia when compared with 8-point capillary determination and that CGM values were generally lower than CBG values (183 ± 37 vs. 183 ± 41 mg/dl; $P = 0.009$). The associations of CGM and capillary blood glucose with A1C were similar and modest in this short-term study (r = 0.40 and 0.39, respectively).

In a randomized, multicenter study of 91 subjects with insulin-requiring diabetes by Garg *et al.*, 5 patients were assigned to wear a DexCom STS system while being either blinded or unblinded to their real-time glucose data.[5] Patients, who were unblinded, exhibited reduced variability in their daily glycemic excursions, as well as a 21% reduction in the amount of time spent hypoglycemic (< 55 mg/dl), a 23% reduction in the amount of time spent hyperglycemic (> 240 mg/dl), and a 26% increase in the amount of time spent in the target glucose range (81–140 mg/dl) compared to the group who remained blinded to their CGM data. In a similar study of 80 patients who used a DexCom CGM system for 3 consecutive 7-day periods, the investigators demonstrated that normal mean glucose concentrations (90–130 mg/dl) between midnight and 7:00 a.m. were associated with an A1C level of < 6%.[11] Importantly, this study also reported a striking degree of accuracy for CGM as compared with capillary blood glucose measurement. Specifically, more than 97% of 6,619 paired capillary-CGM data points fell within the acceptable Clarke error grid regions A and B.

Limitations

All currently available CGM devices measure interstitial glucose. The lag time between when systemic glucose concentration changes appear in the blood and when they appear in the interstitial fluid has been estimated to be between 4 and 26 minutes. This lag results from a delay in equilibration between blood and interstitial glucose and limits the accuracy of CGM for predicting blood glucose concentrations (especially when these concentrations are changing rapidly). The non-linear nature of the lag has made surmounting this limitation difficult. All CGM devices require calibration with plasma glucose at least twice a day, with studies showing improved accuracy with increased numbers of calibrations. Additionally, some studies suggest that accuracy improves when calibrations are performed during times of relative glucose stability rather than during periods when the glucose concentration is rapidly changing. The overestimation of hypoglycemia observed in a number of studies may render CGM inconvenient for people who experience frequent bouts of hypoglycemia, but the technology can also be a very useful tool for people who suffer from hypoglycemia unawareness. In such patients, the lower alarm setting should be chosen carefully so as not to incur too many false alerts while still allowing enough time to verify that blood glucose values are actually low before acting to

correct the hypoglycemia. For this reason, it is argued that trends may be more useful than the absolute value reported. All CGM devices provide information regarding the trend of glucose, indicated by an up or down arrow or by a graphic representation of glucose concentrations over time. These indicators of trend, used together with the point measurements of interstitial glucose, provide the means by which patients can reduce the number and duration of hypoglycemic episodes. The overestimation of hypoglycemia (and to a lesser extent, hyperglycemia) limits the utility of the current generation of CGM devices from working in a "closed-loop" insulin pump system. The idea of a closed-loop system, or artificial pancreas, has long been a goal of many researchers. The rapid development of small, portable CGM devices during the past decade has led many to consider that a closed-loop system may soon become possible. Problems arise, however, when attempting to employ currently available insulin pumps with CGM devices to create a closed-loop system. For an efficient closed-loop system to respond appropriately to a meal, the device would first have to detect a rise in interstitial glucose, which is delayed by at least 10 minutes. This lag needs to be added to the delay in insulin delivery and absorption that occurs with any subcutaneous insulin. These factors, combined with the imprecise accuracy of CGM, significantly reduce the feasibility of using these devices in a closed-loop system.

Summary and Conclusions

The American Diabetes Association has taken a very limited position regarding CGM, stating that, "Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose (SMBG) for selected patients with type 1 diabetes, especially those with hypoglycemia unawareness." It is possible that this statement will be expanded in the future. This new technology can offer patients with diabetes a major advance in improving A1C values and reducing the occurrence of disruptive hypoglycemia. Although the long-term danger of hyperglycemia is an increase in diabetes complications, the short-term hazard of hypoglycemic unawareness can be devastating. An automobile accident, a fall resulting in fracture, or a death from severe hypoglycemia is reason enough to consider using CGM. There is no doubt that CGM technology will continue to improve, just as it has occurred with insulin pump technology during the past 20 years.

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Cite this article as: Pandit K. Continuous glucose monitoring. Indian J Endocr Metab 2012;16:S263-6.

Source of Support: Nil, **Conflict of Interest:** None declared