

Comparing Mythologies: Perspectives on the Utility of Continuous Glucose Monitors in Diabetes Care

BY BRUCE A. PERKINS, MD, MPH, FRCPC

The Diabetes Control and Complications Trial and its subsequent observations unequivocally demonstrated the importance of better glycemic control for reducing the risk of chronic complications in the type 1 diabetes population. As a basic strategy, frequent capillary blood glucose monitoring was considered an essential behaviour for better glycemic control. Most study participants succeeded at establishing a routine that involved monitoring at least 4 times a day. Despite this fundamental accomplishment, those participants who received what is now considered "standard care" – intensive therapy with multiple daily injections or the insulin pump – experienced an excess of severe hypoglycemia and, after study completion, were not able to achieve long-term adherence to target glycemic control.

In the hopes of enabling better self-management skills for such long-term adherence and identifying unforeseen hypoglycemia, continuous glucose monitoring technologies have become available for clinical use. These come in multiple forms, including blinded diagnostic tests supervised by the diabetes care provider or even as unblinded "real-time" glucose monitoring devices used by patients for their own diabetes self-assessment and self-management. Introducing these technologies into clinical practice hinges on the philosophy that having a clearer image of glycemic excursions is the first step for patients and health-care providers in making therapeutic decisions that will lead to improved glycemic control.

Continuous glucose monitoring technologies mark a major step in diabetes care, but they are not magical tools to automate diabetes care. This issue of *Endocrinology Rounds* provides a non-systematic review that will acquaint the reader with common myths and misconceptions about both episodic and continuous glucose monitors. The ultimate goal is to create a set of realistic expectations for patients and their healthcare providers.

Let us compare mythologies and technologies

At the present time in Canada, patients with diabetes may choose from a wide variety of 'episodic' capillary blood glucose meters and supplement these episodic tests with a continuous glucose monitor. The episodic meters generally use test strips that have a coating of glucose oxidase, an enzyme that catalyzes a redox reaction that converts glucose to gluconolactone and hydrogen peroxide, with subsequent generation of an electron charge. The number of electrons produced by the reaction can be quantified because the enzyme is attached to an electrode that measures the resulting charge. In this way, the magnitude of the glucose concentration is estimated, based on the magnitude of electrical charge created by the chemical reaction. Although the episodic monitors have transformed diabetes care since their introduction in the late 1970s by providing a portable and reasonably accurate means to track blood glucose, it is important to acknowledge some of their shortcomings.

- First, they offer only "snapshots" of information at selected times. Under ideal conditions (of temperature, humidity, correct blood sample size), they have an accuracy of 10% to 15% of true glucose values.
- They require multiple calibration steps, including the need for patients to enter a test strip batch calibration code into the meter and to perform regular 'lab correlations' at the time of a plasma glucose blood test in the clinical laboratory.



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- Patients must ‘calibrate’ results to their symptoms; that is, a “normal” blood glucose of 4.5 mmol/L, for example, is at once “abnormal” if accompanied by symptoms of hypoglycemia.
- The cost of individual test strips represents another major limitation in generalizing ideal monitoring behaviours.
- A further unacceptable limitation of conventional episodic monitors, of which many have sophisticated data management functions, is that they fail to provide more advanced feedback to engage patients in diabetes self-assessment and self-management. For example, if the bedtime blood glucose is consistently high despite repeated normoglycemia before dinner, the system could report this observation to the patient and recommend that a change in the dose of dinnertime insulin or of dinnertime carbohydrate be considered (or discussed with the healthcare provider).

Therefore, despite their enormous value in the clinical management of diabetes, the notion that the current episodic blood glucose meters represent a technological ‘gold standard’ is a *myth*. The continuous glucose monitoring technologies as they currently exist by no means overcome these issues. In fact, these systems come with their own set of common myths. The following sections aim to describe the technologies – their pros and their cons – and to dispel common misconceptions.

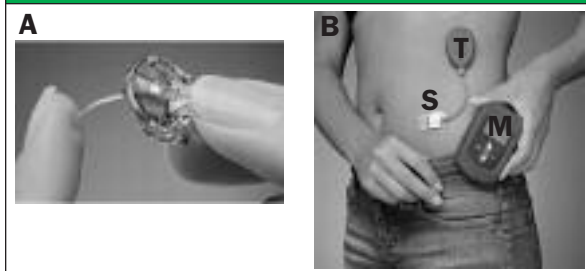
Technologies in development

Reverse iontophoresis: A wristwatch device creates an electrical charge that stimulates movement of interstitial fluid glucose to the skin surface, which is in turn sampled by an abrasive sensor on the underside of the watch. A version of this technology was found to have limitations in accuracy induced by movement of the device and the dilutional effect of sweat on the sensor surface. Although released onto the market as one of the first available continuous glucose monitors, further study found that half of potential glucose measurements were not recorded by the device. Further development of this technology (named the “Glucowatch Biographer”) is ongoing.¹

Impedance spectroscopy: The concept behind this technology is based on the observation that sodium transport over the red blood cell membrane is linked to glucose concentration and flux. As such, a noninvasive electromagnetic device worn on the wrist like a watch can measure the cell membrane impedance fields created by changes in membrane electrical properties on account of altered sodium transport in the face of changing glucose concentration. Although early trials of a device (named the “Pendra”) demonstrated acceptable accuracy, post-marketing studies in Europe have shown exceedingly poor performance.²

Microdialysis: The currently developed (“GlucoDay”) system appears to be designed primarily for the research laboratory setting in that it requires subcutaneous insertion of a hollow microdialysis fiber in (and out) of the

Figure 1: Components of a glucose oxidase enzyme-based CMS



Panel A shows the interstitial glucose sensor, an electrode coated with glucose oxidase and covered with a protective polymer.

Panel B shows the subcutaneously-inserted sensor (S) attached to the transmitter (T) that attaches to the skin with an adhesive patch. Estimated glucose concentration values are sent from the transmitter by radiofrequency transmission to the monitor (M) every 5 minutes for display.

skin, each end connected to a nylon tube. This creates a circuit for a buffer solution to be pumped through the fiber, and then into a biosensor, thus sampling the interstitial fluid glucose. This technology has been evaluated in the setting of a multicentre study.³

Technologies on the market in Canada

Glucose oxidase enzyme-based technology: This technology has made the largest progress in the clinical market. For example, Medtronic Minimed Ltd. has 4 systems – the CGMS Gold, the Guardian, the Guardian Real-Time, and the Paradigm Real-Time – available on the Canadian market. In the United States, Dexcom Inc. has obtained regulatory approval for a short-term sensor and Abbott Inc. has the “Freestyle Navigator” system currently under regulatory review. These systems make use of a subcutaneous electrode coated with glucose oxidase that is placed under the skin by the patient – this ‘sensor’ (Figure 1, Panel A) is exposed to interstitial fluid glucose that reacts with the enzyme, creating an electrical charge that is transmitted to a device that estimates blood glucose concentration (in the same manner as described for episodic capillary glucose monitors above). The earlier versions of these systems required attachment of the monitor directly to the sensor by way of a long insulated wire. The later versions have a small transmitter attached to the subcutaneous sensor that communicates remotely with a monitor that can be worn on a belt or even kept at short distances from the patient - while showering or sleeping, for example (Figure 1, Panel B). Medtronic Minimed’s Paradigm Real-Time system integrates the sensor and the transmitter with an insulin pump that also serves as the monitor, so that a separate device is not necessary.

Typically, the current versions of these sensors need to be changed every 3 days because of ‘biofouling,’ a process that involves protein absorption into the polymer coating of the sensor, thus blocking free diffusion of glucose to the glucose oxidase enzyme layer within. Once placed under the skin, a “warm-up period” of approximately 2 hours is required before the monitor can record and display glucose readings. The patient must perform at

A representative example from the literature⁶ that demonstrates these concepts qualitatively is shown in Figure 3. The figure portrays the reference standard plasma glucose (YSI reading) for an individual who wore 2 CMSs simultaneously. The first observation is that if any individual point along the YSI Reading is chosen in cross-section, the likelihood that one or both of the sensor values has deviated from the reference value is quite high, indicating imperfect *accuracy*. Similarly, if both sensor curves – when examined in cross-section at individual points in time – do not overlap dependably, this indicates imperfect *precision*. However, examination of the entire longitudinal trend of reference YSI readings over the day demonstrates that the global performance appears acceptable and that, overall, each sensor represents the general direction and pattern of glycemic excursions exceptionally well. Whether this feature is sufficient to overcome imperfect accuracy and imperfect precision in clinical applications requires examination of the clinical trial literature.

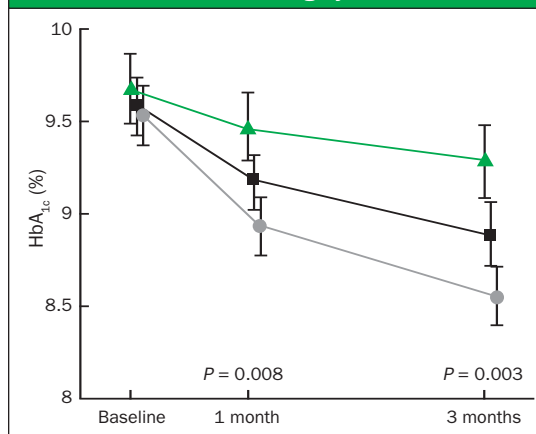
Clinical trials of enzyme-based CMSs

Over 60 randomized controlled trials using CMSs have been published in the medical literature. The majority of these studies use the readings as an outcome measure rather than being designed specifically to test the effectiveness of the systems themselves on glycemic control. For example, “areas under the curve” can be calculated to better quantify the magnitude of excursions into the hyperglycemia and hypoglycemia range as an outcome measure in drug trials. These calculations are more accurate than measurements of the glycosylated hemoglobin A1c as an integrated measure of glycemic exposure.⁷

Several randomized controlled trials investigating the frequency and magnitude of glycemic excursions or glycosylated hemoglobin A1c have been published. These studies tend to include <50 subjects,⁸⁻¹¹ although several trials have greater power.¹²⁻¹⁵ The most common design was a comparison of “blinded” versus “unblinded” continuous glucose monitoring, or groups with and without programmed hypo- or hyper-glycemic alerts¹² over short study intervals up to 3 months. Decreased glycemic excursions¹²⁻¹⁴ and decreased glycosylated hemoglobin A1c^{8,9,11,15} were commonly observed in those with unblinded monitors or those set with alerts. However, some controversy exists since a 6-month crossover trial in 30 children with type 1 diabetes demonstrated no detectable glycemic benefit.¹⁰

A particular focus in the literature that evaluates the clinical impact of unblinded (or the so-called “real-time”) systems is of the greatest importance because it is this technology that will permit patients to participate more in diabetes self-evaluation and self-management. One short-term study demonstrated improvement in glycemic excursions, but was

Figure 4: Change in glycosylated hemoglobin A1c (HbA1c) in a randomized clinical trial of an unblinded (“real-time”) glucose oxidase enzyme-based continuous monitoring system.¹⁵



The graph shows the mean \pm SE HbA_{1c} values at baseline, 1, and 3 months for the control group who used conventional episodic capillary glucose monitoring (●), the biweekly continuous monitoring group (■), and the group that wore continuous monitoring systems for 3 months (▲). P values correspond to the difference in change from baseline between the continuous and control groups.

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inadequate in duration (9 days) to justify evaluation of glycosylated hemoglobin A1c.¹⁴

A recent report of an unblinded CMS (the Guardian Real-Time system), evaluated in a sufficiently long study of 3 months duration, implies that there is a major clinical benefit for individuals with suboptimal glycemic control.¹⁵ This study investigated 156 adult and pediatric subjects in a 3-arm randomized trial: The first arm received 3 months of continuous monitoring, the second arm wore sensors only for 3 days every 2 weeks as a self-evaluation test, and the third arm – the control arm – simply continued conventional episodic capillary blood glucose testing. From a mean group with a glycosylated hemoglobin A1c value of approximately 9.5%, the first and second arms of the study (corresponding to subjects who undertook continuous and biweekly continuous monitoring, respectively) experienced mean declines in glycosylated hemoglobin A1c of 1.0 and 0.7, respectively, significantly different in combination as compared to reductions in the control arm of 0.4% (Figure 4).

The issue of hypoglycemia “alarms” and “alerts”

Although randomized clinical studies demonstrated less exposure to hypoglycemia when using an (unblinded) CMS, there appears to be general agreement that the accuracy of these systems is not sufficient enough to provide perfectly reliable hypoglycemia alarms without substantial false positive and false negative alarms.⁵ In current clinical use,

confirmation of alarms is recommended by performing an additional capillary blood glucose test before therapeutic intervention or corrective action is taken. Patients are often frustrated by false positive alarms that wake them up at night, that are subsequently not confirmed by capillary testing and, on review of the visual graph of glucose values on the monitor, they appear to be stable. However, a hypoglycemia “alert” can be of major benefit. Unlike an alarm, which is meant to indicate that the blood glucose is in the hypoglycemia range at the moment of the alarm, an “alert” signals when the glucose level is dropping quickly, indicating that the risk of subsequent hypoglycemia is high. In this way, a patient can be alerted to a dropping glucose level, examine the visual graph of glucose trends on the monitor, and take corrective action if necessary. Clearly, the “alert” primarily benefits the patient who has a good working knowledge of target blood glucose levels and an understanding of peak insulin action.

Implications for patients and diabetes caregivers – the pros and cons

The ultimate goal of a CMS is the provision of sufficiently accurate and precise glucose readings that can be immediately used to adjust therapy (eg, a closed-loop device that estimates blood glucose and delivers insulin safely and independently).¹⁶ However, the current interstitial enzyme-based technologies do not have sufficient operating characteristics to be used within such a closed-loop system. In fact, the physiological lag error between changes in blood and interstitial fluid glucose concentrations requires the calibration of current CMSs with capillary blood glucose measurements (that have their own inherent inaccuracies). A number of potential solutions, such as local pressure modulation techniques at the site of the subcutaneous sensor to improve blood flow and subsequent glucose concentration equilibration between compartments, are being investigated.¹⁷ The reader is referred to the two recent publications shown in abstract form at the end of the issue.

Despite the fact that current CMSs are not sufficiently accurate to be used in closed-loop insulin delivery systems or even for making therapeutic decisions independently of capillary blood glucose calibrations, they do provide substantial benefit. First, as discussed above, they have an impact on reducing hypoglycemia, glycemic excursions, and even glycosylated hemoglobin A1c in patients with suboptimal control. Furthermore, there are very practical applications for the continuous data. For example, the data can be used to evaluate the effects of exercise and strategize the timing of insulin adjustments and extra carbohydrates relative to activity. It can also be used to assess basal insulin

rates when initiating and maintaining insulin pump therapy, to evaluate the effects of specific kinds of foods, and to refine the prescribed carbohydrate-to-insulin ratio.

In clinical observation and in small observational studies, the unblinded systems provided patients with immediate feedback about food choices and carbohydrate counting. As a result, patients tended to have much smaller glycemic excursions related to meals within 9 days, likely due to increased accountability for meals. In essence, many patients are not able to sufficiently enhance their diabetes knowledge because of the limited feedback that episodic capillary blood glucose monitors provide. The CMSs may, in part, overcome this shortcoming.

However, CMSs have limitations above and beyond those related to accuracy and precision. The systems are labour-intensive in that they currently require insertion of a subcutaneous sensor every 3 days. In addition, they do not eliminate the need for capillary blood glucose testing. They may also create a situation of information overload that some patients and caregivers are unable to overcome. Finally, the immediate cost of the monitors and sensors far outweigh the current costs of conventional glucose monitoring, an issue that remains to be reconciled with insurance providers.

Conclusion

Although the current, conventional, episodic, blood glucose monitors have made an enormous impact on the quality of diabetes care, certain mythologies exist relating to their accuracy and reliability. Certainly, they do not represent an ideal reference standard for validation of new monitoring technologies. Similarly, the newer continuous glucose monitoring technologies have their own set of misconceptions regarding accuracy and reliability and are by no means ready for incorporation into a closed-loop insulin delivery device. However, they have existing features that constitute an important step towards helping to establish the critically important self-management skills necessary for patients to adhere to long-term glycemic control.

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Abstracts of Interest

Continuous glucose monitoring and closed-loop systems

HOVORKA R, DIABETES MODELLING GROUP, CAMBRIDGE, UK.

BACKGROUND: The last two decades have witnessed unprecedented technological progress in the development of continuous glucose sensors, resulting in the first generation of commercial glucose monitors. This has fuelled the development of prototypes of a closed-loop system based on the combination of a continuous monitor, a control algorithm, and an insulin pump. **METHOD:** A review of electromechanical closed-loop approaches is presented. This is followed by a review of existing prototypes and associated glucose sensors. A literature review was undertaken from 1960 to 2004.

RESULTS: Two main approaches exist. The extracorporeal s.c.-s.c. approach employs subcutaneous glucose monitoring and subcutaneous insulin delivery. The implantable i.v.-i.p. approach adopts intravenous sampling and intraperitoneal insulin delivery. Feasibility of both solutions has been demonstrated in small-scale laboratory studies using either the classical proportional-integral-derivative controller or a model predictive controller. Performance in the home setting has yet to be demonstrated.

CONCLUSIONS: The glucose monitor remains the main limiting factor in the development of a commercially viable closed-

loop system, as presently available monitors fail to demonstrate satisfactory characteristics in terms of reliability and/or accuracy. Regulatory issues are the second limiting factor. Closed-loop systems are likely to be used first by health-care professionals in controlled environments such as intensive care units.

Diabet Med 2006;23:1-12.

Continuous glucose monitoring: key challenges to replacing episodic SMBG

STOUT PJ, RACCHINI JR, HILGERS ME, NOUJAIM SE, MILPITAS, CALIFORNIA

Lag between blood and interstitial fluid (ISF) glucose levels can contribute significantly to accuracy errors in current and anticipated continuous glucose monitoring systems. Mitigating this physiological lag can be an important and useful means for improving the accuracy, and hence the clinical utility of continuous glucose monitors. In a test of 22 subjects with diabetes, two ISF samples (control and mitigated) and a finger capillary blood glucose sample were taken and compared. The methodology presented here of using a pressure modulation technique to create an elevation in blood flow holds promise for significantly mitigating one of the most significant components of accuracy error for continuous monitoring systems.

Diabetes Res Clin Pract 2006;74 Suppl 2:S97-S100.

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