

# New Developments in Home Glucose Monitoring: Minimizing the Pain

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## ABSTRACT

Less invasive blood glucose (BG) monitoring offers an attractive alternative to current fingerstick monitoring techniques. BG sampling from other less sensory nerve-rich sites is currently available. Continuous monitoring of interstitial glucose can provide information regarding the direction of glucose changes and alarms for hypoglycemia, and can detect unrecognized trends in glucose values. Some promising approaches to noninvasive monitoring of glucose are discussed, along with some of their potential limitations. The availability of these technologies to measure glucose non-invasively will likely result in improved patient outcomes.

## RÉSUMÉ

Les méthodes de surveillance de la glycémie moins effractives que la piqûre au bout du doigt sont très intéressantes. Le prélèvement de sang à des endroits où se trouvent moins de nerfs sensoriels est actuellement possible. La surveillance continue du glucose interstitiel peut renseigner sur les modifications de la glycémie, signaler les hypoglycémies et déceler les tendances de la glycémie. Cet article traite de techniques prometteuses de surveillance non effractive de la glycémie ainsi que de certaines de leurs limites. Ces techniques aboutiront vraisemblablement à une amélioration du devenir des patients.

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## INTRODUCTION

Maintenance of good glycemic control effectively reduces the incidence of complications of diabetes. Improvements in glycemic control, however, are often at the expense of an increased incidence of hypoglycemia. In the landmark Diabetes Control and Complications Trial in patients with type 1 diabetes, the intensive blood glucose (BG) control group had a 2- to 3-fold increase in the number of severe hypoglycemic episodes (1). The risk of hypoglycemia becomes even greater as many patients develop hypoglycemia unawareness. Frequent BG monitoring is the primary means of preventing severe hypoglycemic events. Current fingerstick methodology, however, is not well tolerated by patients. Despite recommendations for frequent home BG monitoring, it is estimated that most patients treated with insulin check their BG <1 time per day (2,3). Noninvasive BG monitoring represents a potential way to increase compliance with BG monitoring. Three general approaches to home glucose monitoring are described: 1) noncontinuous and minimally invasive; 2) continuous but invasive; and 3) continuous and noninvasive (Table 1).

## NONCONTINUOUS AND MINIMALLY INVASIVE BG MONITORING

Current BG monitoring using test strips is dependent on the glucose oxidase assay. The assay requires sufficient blood volume that, until recently, necessitated fingerstick puncture. Several companies have developed products that can assay BG levels using smaller blood volumes. This technology has enabled blood sampling from sites other than the sensory nerve-rich fingertips with specifically designed lancing devices for sampling from the arms, legs and other sites. Some examples of this technology include FreeStyle<sup>®</sup> by TheraSense (Alameda, California, United States [US]), AtLast by Amira Medical (Scotts Valley, California, US), Precision<sup>™</sup> Sof-Tact<sup>™</sup> by MediSense<sup>®</sup> Products, Abbott

Laboratories (Bedford, Massachusetts, US) and OneTouch<sup>®</sup> Ultra<sup>®</sup> by LifeScan, a Johnson & Johnson company (Milpitas, California, US).

Recently, concerns have been raised regarding a lag time between BG samples from alternate sites and fingerstick BG results that could be clinically significant in the setting of rapid BG fluctuations (4). In particular, fingerstick BG values drop faster than measures from the arm, with a time lag of approximately 35 minutes (4,5). Therefore, it has been recommended that alternate site testing on the arm be reserved for preprandial testing or testing >2 hours after a meal, an insulin dose or physical exercise, since BG testing from the arm may fail to detect hypoglycemia (6). The potential to miss hypoglycemic events with alternate site testing renders this approach less appealing than the fingerstick approach (6).

Current BG monitoring still depends on obtaining blood samples. Skin puncture to the depth of the capillaries involves disruption of nearby sensory nerves, resulting in patient discomfort. Glucose from capillaries diffuses across the endothelium to the interstitial space from which it can ultimately be taken up by target tissues. The sensation-free stratum corneum (uppermost layer of dead skin) is the only barrier to accessing interstitial glucose. Several technologies described below have been utilized to bypass this micron-thin barrier. However, interstitial glucose levels may not always coincide with BG values. There can be a lag between transport of glucose from capillaries to the interstitial space. Postprandially, BG rises prior to interstitial glucose and, during hypoglycemia, interstitial glucose declines prior to BG (7-12). This lag is further prolonged by the amount of time required for glucose levels to be assayed by some methodologies. Error can also be introduced through the influence of changes in temperature and perspiration on the interstitial space. Despite these potential barriers, the measurement of interstitial glucose has been the basis for virtually all noninvasive technologies.

**Table 1. Approaches to home glucose monitoring**

### *Noncontinuous and minimally invasive*

- Alternate site testing (e.g. OneTouch<sup>®</sup> Ultra<sup>®</sup>, LifeScan)

### *Continuous but invasive*

- Needle sensor glucose oxidase system (CGMS<sup>®</sup> System Gold<sup>™</sup>, Medtronic MiniMed)
- Micropore system (SpectRx, Inc.)
- Microdialysis system (Roche Diagnostics)

### *Continuous and noninvasive*

- Iontophoresis (GlucoWatch<sup>®</sup> G2<sup>™</sup> Biographer, Cygnus, Inc.)
- Spectroscopy
- Sonophoresis

CGMS = continuous glucose monitoring system

## CONTINUOUS BUT INVASIVE GLUCOSE MONITORING

Continuous glucose monitoring offers several advantages over current measurement of glucose levels at individual time points. Information regarding the vector of glucose changes can have significant clinical implications. The management of a glucose value of 8.4 mmol/L during a rapid decline in glucose would clearly be different from when glucose values are known to be rising rapidly (Figure 1). Currently, no information about the direction of changes in glucose levels is available from periodic testing. Continuous glucose monitoring could uncover hidden glucose trends such as unrecognized nocturnal hypoglycemia leading to fasting hyperglycemia (Somogyi phenomenon). Hypoglycemia alarms could alert patients with hypoglycemia unawareness. Measurement error is also decreased with continuous glucose monitoring since the range of possible glucose values is

biologically limited by the preceding value. The overall goal of continuous glucose monitoring would be to improve glycemic control. Three of the more promising minimally invasive approaches to continuous glucose monitoring include a needle sensor system (Continuous Glucose Monitoring System [CGMS<sup>®</sup>], System Gold<sup>™</sup>, Medtronic MiniMed, Northridge, California, US), micropore system (SpectRx, Inc., Norcross, Georgia, US) and microdialysis system (Roche Diagnostics, Mannheim, Germany).

### Needle sensor system

The CGMS by Medtronic MiniMed utilizes a subcutaneous (SC) needle sensor that transmits data through a wire to a monitor worn by the patient (13-15). Glucose is assayed using the glucose oxidase method and is thus sensitive to changes in the local substrates glucose and oxygen. In general, SC needle insertion may cause local inflammation that can lead to a drift in glucose levels surrounding the needle sensor (16). This glucose drift necessitates frequent (minimum of 3 times per day) calibration of the CGMS with fingerstick BG testing. Although the device is currently available in the US, no read-out of glucose values is available to the patient. The device is worn by the patient for 3 days and brought to their health-care provider, where glucose values are downloaded for retrospective analysis. This is similar to the use of a Holter monitor for heart rate measurements. Medtronic MiniMed is currently upgrading this device to a more consumer-friendly model (the Guardian<sup>™</sup>) where glucose readings are transferred from the sensor to the monitor by radio frequency. Continuous glucose monitoring, however, will still be at the expense of fingerstick calibration 3 times per day. Difficulties in calibration have been reported despite frequent fingerstick calibration (17). Despite these limitations, physician utilization of this device has uncovered unrecognized glucose trends (13) and resulted in improved glycemic control (14,15). CGMS is likely to be most useful as an adjunct to fingerstick measurements to detect unrecognized glucose trends, including nocturnal hypoglycemia, and for the adjustment of insulin infusion pump delivery schedules.

### Micropore system

SpectRx, Inc. has developed a micropore system whereby a laser porator generates tiny holes in the stratum corneum (approximately the width of a human hair) through which interstitial glucose is extracted and assayed. A suction cup patch is applied over these stratum corneum pores, and interstitial glucose is measured using a disposable biosensor patch. Glucose measurements are performed externally and, therefore, are not subject to the same glucose drift phenomenon observed with SC sensors. Fingerstick calibration is performed once daily, and glucose values obtained every 6 seconds are transmitted by radio frequency to a remote display. The sensor has a thermometer that makes calibration adjustments for changes in temperature. The poration and subsequent

glucose values appear to be accurate for 48 to 72 hours (18). Pediatric studies are currently underway and have focussed on the durability of this device in the setting of physical activity.

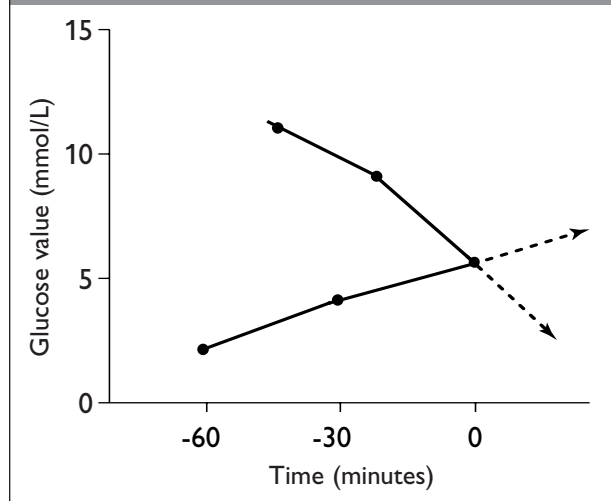
### Microdialysis system

Microdialysis can also be utilized for subcutaneous continuous glucose monitoring (SCGM). One example is the SCGM system by Roche Diagnostics, which consists of a microdialysis catheter and a portable extracorporeal electrochemical glucose sensor. A pump circulates a liquid through a tube into which interstitial glucose diffuses. Glucose values are displayed every minute over a 3-day period, but there appears to be a significant drift in glucose values (19). Calibration requires correction for the time of fluid transportation from the catheter to the extracorporeal sensor (31 minutes, based on a linear 1-point calibration model using a single fingerstick BG value obtained after an initial equilibration period of approximately 4 to 5 hours) (19). A recent study of 23 patients with insulin-treated type 1 or type 2 diabetes demonstrated an intra-individual mean absolute difference of  $14.8 \pm 9.9\%$  between glucose values obtained using the SCGM system and capillary BG (19). Continuous monitoring of glucose with the microdialysis system was effective in detecting many hypoglycemic episodes that were unrecognized by frequent (up to 7 times per day) BG monitoring. This technique offers the advantage of requiring only 1 fingerstick every 72 hours for calibration purposes, but it is still under clinical investigation.

## CONTINUOUS AND NONINVASIVE GLUCOSE MONITORING

Patient preference clearly points toward a completely noninvasive method for glucose monitoring. Noninvasive monitoring also offers the potential to avoid glucose drift that can

**Figure 1. The directional vector of glucose changes prior to a specific glucose value (i.e. time=0) can be valuable in predicting future glucose levels**



occur due to local inflammation, angiogenesis and substrate utilization (16). Three promising approaches are highlighted: iontophoresis, infrared spectroscopy and sonophoresis.

### Iontophoresis

The GlucoWatch® G2™ Biographer (Cygnus, Inc., Redwood City, California, US) utilizes reverse iontophoresis to extract interstitial glucose for measurement within a watch-like device. The watch generates a small electrical field that attracts sodium ions along with water and glucose across the stratum corneum. Micromolar concentrations of diffused glucose are then assayed within an AutoSensor using glucose oxidase. A 2-hour warm-up period is required prior to calibration with a single fingerstick BG measurement. Interstitial glucose levels are then measured up to 3 times per hour for the subsequent 12 hours (20). The system is capable of detecting events that may produce an erroneous result, such as excessive perspiration. In such a case, the measurement is skipped. In clinical trials, approximately 13% of values were missed during a 12-hour period (20). Patients may note some local erythema at the site of GlucoWatch placement; therefore, the manufacturer recommends site rotation as well as avoidance of scraped, cut or sunburned areas. The GlucoWatch can be worn while washing the hands, but must be removed for showering.

**Table 2. Sensitivity and specificity of hypoglycemia detection with conventional FS BG measurement (sensitivity only) and the GlucoWatch® G2™ Biographer (Cygnus, Inc.) (Adapted from reference 21)**

Method	Sensitivity (%)	1-Specificity (false positive rate) (%)
<b>Conventional</b>		
2 FS per day	14	NA
4 FS per day	39	NA
<b>GlucoWatch® G2™ Biographer low-interstitial glucose alert setting (mmol/L)</b>		
3.9	24	1
5.0	62	6
5.6	75	10
6.1	86	16

BG = blood glucose

FS = fingerstick

NA = not applicable

Patients who require constant monitoring will need 2 GlucoWatches so that 1 can be calibrated while the other comes to the end of its cycle. The US Food and Drug Administration approved the device in March 2001, and it is currently available in the US and the United Kingdom.

Continuous glucose monitoring offers the opportunity to notify patients when hypoglycemia has occurred. Analysis of data obtained with the GlucoWatch Biographer indicates that setting the glucose cutoffs for alarming patients of hypoglycemia may be a complex decision (21). A glucose cutoff of 3.9 mmol/L only captured 24% of hypoglycemic events; however, the specificity of these alarms was excellent (99% [Table 2]). If the alarm threshold is increased, the sensitivity is improved at the expense of a lower specificity. For example, setting the alarm at 5.6 mmol/L yielded a sensitivity of 75% with a specificity of 90%. The sensitivity of the GlucoWatch is considerably better than concomitant results observed with noncontinuous fingerstick BG measurements performed twice (14%) or 4 times per day (39%). Clearly, the alarm threshold will need to be individualized.

The GlucoWatch Biographer may be beneficial for a specific patient population, such as those with frequent problems of hypoglycemia and/or hyperglycemia, with hypoglycemia unawareness or who experience a disruption in their normal routine (e.g. vacation, travel, illness), or to provide additional information to help solve issues related to poor glycemic control. The device is still limited by skipping approximately 10% of readings, cost (approximately US \$650.00 for the device itself and \$4.00 per 12-hour AutoSensor) and local skin irritation after its use.

### Infrared spectroscopy

Various spectroscopic techniques have been explored for noninvasive continuous glucose monitoring. Glucose absorption of energy in the near-infrared range has been the most widely studied methodology (22). Near-infrared spectroscopy uses an external source with a wavelength that is just above that of the visible spectrum. The light passes through or is reflected by a body part. Light absorbed at selected wavelengths is then analyzed for each interstitial glucose level, and a multivariate processing algorithm is used to develop a calibration curve. This technology is currently used in oximetry to measure the oxygen saturation of blood. For spectroscopy to be applicable to glucose monitoring, the spectral signal of glucose must be different from that of other molecules and, at the same time, the signal-to-noise ratio must be high enough to permit differentiation between signals generated by other chemical constituents. Only approximately 1/10 000 of the spectral absorption of infrared light in vivo is by glucose; both water and hemoglobin significantly absorb infrared light. Frequent calibration is therefore required to compensate for any changes in tissue hydration, body temperature, hemoglobin level and, potentially, for medications that absorb infrared light. Nevertheless, a prototype

utilizing this technology was marketed in the European Union to augment results from fingerstick BG measurements (Diasensor, Biocontrol Technology, Inc., Indiana, Pennsylvania, US), and another prototype has recently been described (22). The Diasensor, however, requires a 60-day calibration with 2 fingersticks per day, and subsequent readings are only reliable to provide trends; individual measurements cannot be used to adjust insulin or detect hypoglycemia. It is unclear at this time whether further development of the Diasensor will continue.

### Sonophoresis

Sonophoresis utilizes low frequency ultrasound (5 to 100 kHz) to cause temporary cavitation of the stratum corneum. Cavitation induces aqueous channels to form in the stratum corneum through which small molecules, such as glucose, can diffuse. The degree of cavitation is inversely proportional to the applied ultrasound frequency. The effectiveness of ultrasound-induced cavitation can be easily assessed by reductions in skin resistance. Both in vitro and in vivo studies have demonstrated that low frequency ultrasound applied to human cadaveric skin or intact rat skin substantially increases glucose flux across the skin (23). In initial clinical trials, a single application of low frequency ultrasound for <2 minutes resulted in consistent glucose diffusion across the skin for 12 hours, with good correlation of glucose values obtained over 4 hours to standard BG measurements (23). The magnitude of glucose flux was approximately 25 times higher than that generated by iontophoresis. This greater flux may translate to increased accuracy and shorter sampling time. Home application of this technology is envisioned to involve a handheld ultrasound generator applied to the wrist at the beginning of the day. Diffused glucose could then be assayed continuously with a watch-like biosensor. Future studies are required to determine the effect of repeated ultrasound application to human skin and the possibility of calibrating glucose values to another relatively stable diffusible analyte (obviating the need for fingerstick BG determinations).

### CONCLUSION

Several promising approaches are currently under investigation to make glucose monitoring more patient friendly and improve clinical outcomes. Blood sampling from less sensory nerve-rich sites is currently available but may be unreliable during times of rapid BG changes. Continuous glucose monitoring clearly offers substantial promise in alerting patients of hypoglycemia and detecting unrecognized trends, which could lead to better overall glycemic control. These technologies are limited by the current need for frequent calibration with fingerstick BG measurements. Future studies will likely attempt to improve the calibration process, perhaps through measurement of a second, relatively constant metabolite that could be used as a reference value. Another potential concern is the difference between interstitial

glucose and BG values when rapid fluctuations in glucose level are occurring. Techniques that require a significant length of time to perform the glucose oxidase assay add to the biological lag of glucose flux between the capillaries and the interstitial space. Studies will need to evaluate whether treatment protocols using interstitial glucose values will ultimately result in superior clinical outcomes.

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