# Future Perspectives in Glucose Monitoring Sensors

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## Abstract

The prevalence of diabetes is increasing. Improved glucose control is fundamental to reduce both long-term micro- and macrovascular complications and short-term complications, such as diabetic ketoacidosis and severe hypoglycemia. Frequent blood glucose monitoring is an essential part of diabetes management. However, almost all available blood glucose monitoring devices are invasive. This determines a reduced patient compliance, which in turn reflects negatively on glucose control. Therefore, there is a need to develop noninvasive glucose monitoring devices that will reduce the need of invasive procedures, thus increasing patient compliance and consequently improving quality of life and health of patients with diabetes.

## Keywords

Diabetes, continuous glucose monitoring, noninvasive glucose monitoring, HbA1c

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Blood glucose monitoring is fundamental in the management of diabetes and is essential to optimize glycemic control. Achieving optimal glucose control is important in reducing the risk for significant long-term microvascular (nephropathy, retinopathy) and macrovascular (cardiovascular disease) complications, as well as neuropathy. Intensive insulin therapy and frequent blood glucose determinations are recommended to achieve glucose objectives in Type 1 diabetes patients.[1] Self-monitoring of blood glucose (SMBG) is performed by obtaining a capillary blood sample by means of a lancing device and then measuring the blood glucose employing a glucose meter. The obtained result represents the blood glucose at the moment when the blood was drawn. This method provides an accurate determination the glucose levels; however, significant oscillations in blood glucose may be ignored, hindering the achievement of an optimal glycemic control.[2] Furthermore, SMBG entails a significant number of daily punctures that many patients find uncomfortable and painful.

Continuous glucose monitoring (CGM) systems measure interstitial fluid glucose levels providing continuous information reflecting blood glucose levels. This continuous monitoring may recognize glucose oscillations that may otherwise remain unidentified with SMBG alone. Currently, the use of CGM is not common practice.[3] CGM is considered to be particularly useful for children (to reduce the often very high number of finger punctures in this group), for patients with poorly controlled diabetes, for pregnant women in whom tight glucose control is essential with respect to the outcome of pregnancy, and for patients with hypoglycemia unawareness (to prevent dangerous episodes of hypoglycemia).[4,5]

A recent meta-analysis by Langendam et al.[4] shows that there is limited evidence for the effectiveness of realtime CGM (RT-CGM) on glycemic control. However the reduction in glycated hemoglobin (HbA1c) levels seems to be related to actual CGM use. After 12 months, those patients who used their CGM frequently had a significantly lower HbA1c level compared with patients who showed low or no sensor usage.[4] Furthermore, a recent consensus statement from the European Society for Pediatric Endocrinology, the Pediatric Endocrine Society and the International Society for Pediatric and Adolescent Diabetes declared that the use of RT-CGM may be appropriate for motivated children and youth of all ages provided that appropriate support personnel are available.[6]

CGM therefore provides detailed information on glucose oscillations and trends. This allows patients to manage their diabetes more successfully. Several CGM systems are commercially available. Two types of CGM systems can be identified according to the way information is delivered:

- Retrospective systems that measure the glucose concentration during a certain time span: the information is stored in a monitor and can be downloaded in a second moment.
- RT systems that continuously provide the actual interstitial glucose concentration and trend on a display.

CGM devices can be further classified into three categories: invasive, minimally invasive, and noninvasive. Sensor placement/invasiveness depends on the its transduction mechanism.[7,8]

## Current (Invasive) Continuous Glucose Monitoring Systems

There are four RT-CGM devices approved by the US Food and Drug Administration (FDA) and clinically used: DexCom® SEVEN® PLUS (San Diego, California, US), Medtronic MiniMed Paradigm® and Guardian® REAL-Time (Minneapolis, Minnesota, US), and Abbott Diabetes Care FreeStyle

Navigator (Maidenhead, Berkshire, UK). Each system consists of a glucose oxidase-based electrochemical sensor, which is placed subcutaneously. Interstitial glucose measurements are then sent continuously from the sensor to a receiver through wireless technology.

The DexCom SEVEN PLUS CGM is a wireless device with a sensor, approved for 7-day wear in 2010, inserted into the subcutaneous tissue of the abdomen. A transmitter connects to the sensor that sends the information to the receiver to display glucose measurements every 5 minutes. There is a 2-hour start-up period during which no glucose values are presented and requires calibrations by SMBG every 12 hours. This system also has alarms that can be set at specified levels to alert the patient of a hypoglycemic or hyperglycemic glucose level. The model also displays the glucose rate of change and trends of blood glucose over 1, 3, 6, 12, and 24 hours. One feature that distinguishes it from other models is the ability to enter times of meals, insulin administration, and physical activity, providing a more complete picture of the potential causes of glucose excursions. However, acetaminophen interferes with the glucose measurements and should not be consumed during sensor wear. This device can be used for patients using continuous subcutaneous insulin infusion (CSII) in combination with the Animas® Vibe™ pump, which represents one of the two available CGM-enabled devices along with the Medtronic Paradigm pump. A new and more accurate G4 Platinum version was recently approved by the European Medicines Agency (EMEA).

The Medtronic MiniMed Enlite CGM consists of an external monitor and a subcutaneous sensor that must be calibrated by SMBG every 12 hours, approved for 6-day wear. This system also requires a 2-hour warm-up time before blood glucose values are displayed, after which readings are displayed every 5 minutes. This device can be used for patients using CSII and requires only one device that works as both the insulin pump and the CGM. Like the Animas Vibe, although the monitor is the same for both systems, it requires two separate insertion sites separated by at least a few centimeters: one for the CGM and one for the pump. The device presents glucose trend graphs over 3 and 24 hours as well as hypoglycemic and hyperglycemic alerts with trend arrows. These devices also have the predictive alarm feature that can alert the patient when the rate of change and current glucose value will lead to a hypoglycemic or hyperglycemic event within a specified time period. Meals and insulin administrations can be entered. The Medtronic Minimed VEO sensor-augmented pump is currently the only device available that features the 'low glucose suspend' (LGS) function, which suspends the insulin infusion for 2 hours when glucose values are below a pre-established glucose threshold. The goal of a threshold suspend device system is to help reduce the severity or reverse a dangerous drop in blood glucose level (hypoglycemia) by temporarily suspending insulin delivery when the glucose level falls to or approaches a low-glucose threshold.

The Abbott Diabetes Care FreeStyle Navigator CGM was approved by the FDA in March 2008 and started distribution in 2011. This device also contained a subcutaneous sensor with an external monitor requiring calibrations at 10, 12, 24, and 72 hours. Although there are fewer total calibrations, the first blood glucose measurement is not displayed until after the first calibration is entered at 10 hours. Afterwards, it displays an updated glucose measurement every minute. A more recent version with a 1-hour warm-up period has been approved by the FDA, but is not currently available in the US. The Navigator alerts current and predictive lows and highs and displays 2, 4, 6, 12, and 24-hour trend graphs. Meals and insulin administrations can also be entered. The sensors are approved for 5-day continuous wear. A second-generation device is under study.

A different approach of invasive sensors includes microdialysis technology. In this context, a catheter housing a dialysis membrane inserted within the subcutaneous tissue to continuously pass glucose-free isotonic fluid across the skin. During passage through the skin, the isotonic fluid collects glucose that is assayed externally using optical or electrochemical techniques. Along these lines, catheter-shaped sensors have also been introduced, wherein the sensing element is located at the catheter tip, while the transmitter is located at its other end, which sits outside the skin. Similarly, a disposable, invasive optical fiber has also been introduced that is capable of percutaneous glucose monitoring via spectroscopic measurements.[9]

RT information by CGM devices can be used by patients to adjust their insulin doses and can be downloaded by physicians to provide an overall picture of glucose control and discuss it interactively with their patients. The adjustable hypo- and hyperglycemia alerts may be valuable when patients usually do not check their SMBG (i.e. during sleep or while driving) helping to prevent potentially dangerous glucose excursions. CGM allows patients to actively evaluate the effects of lifestyle decisions on glucose excursions, allowing them to apply modifications to certain behaviors to ensure adequate glucose control in future similar circumstances, and progressively reduce HbA1c.[10] These devices have been shown to help minimize time spent in hypoglycemic and hyperglycemic ranges and reduce glucose excursions.[6]

Presently, CGM use is approved only as a complementary tool alongside SMBG, requiring patients to confirm the CGM information with a fingerstick determination before making any therapeutic decisions.[11] Furthermore, the sensors need to be calibrated when glucose values are most stable in order to display the most accurate glucose measurements. Approximately 5–20 % of patients suffer from erythema, edema, or skin irritation due to the sensor adhesive.[10,12,13] Another disadvantage of CGM is the time lag between the blood glucose value and the interstitial glucose value. The time lag is related to errors in SMBG and is especially accentuated with a higher rate of change of glucose greater than 2 mg/dL/minute (0.1 mmol/l/minute). Additionally, patients may be tend to overcorrect hyperglycemia by repeated insulin boluses or overcorrect hypoglycemia by multiple carbohydrate doses.[14] This may ultimately lead to an increased risk for hypo- and hyperglycemia. Consequently, patients should be adequately trained on the use of CGM devices to avoid misinterpretation of continuous data.

While CGM requires proper training and time from physicians to interpret and analyze the data, it has been shown to be advantageous to patients by increasing their time spent in euglycemic range. This can improve the patient's glycemic control and can ultimately help reduce HbA1c.[15–17]

Despite the benefit of multiple information provided by RT-CGM (i.e. glucose trends and trend alerts, alerts for hypo-/hyperglycemia, predictive alerts) it has not been embraced. Several reasons such as complexity, inaccuracy, inappropriate expectations, invasiveness, cost, pain, discomfort, risk for infection, and interference with daily activities remain significant drawbacks.[18] These matters have hampered motivation

## Table 1: Technologies for Noninvasive Diabetes Management[7]

| Technology Employed | Company | Device | Target Site | Characteristics |
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| A) Main devices with substantiated claims: | | | | |
| Reverse iontophoresis | Animas Technologies (Cygnus Inc.) | GlucoWatch© G2 Biographer | Wrist skin | **Advantages:** CE and FDA approved; takes into account the skin temperature and perspiration fluctuations; alarm and trend indicators for rapid changes in glucose readings; event marking, data download, software analysis, and data-storage capacity<br>**Disadvantages:** Expensive; requires 2–3 hour warm-up period, calibration using a standard blood glucose meter and replacement of disposable pad every 12 h; difficulty in calibration; inaccuracy due to subject's movement, exercising, sweating or rapid temperature changes; cannot be used in water; skin irritation was the main drawback; it shuts down automatically in cases of sweating, works better at high glucose levels and does not reliably detect hypoglycemia |
| Bioimpedence spectroscopy | Biovotion AG (Solianis Monitoring AG; Pendragon) | GlucoTrack™ | Wrist skin | **Advantages:** CE approved; data downloading via USB, data analysis, software, data-storage capacity and long-lasting battery; alerts for rapid changes in glucose concentration and hypoglycemia; self-correction for changes in impedance due to variations in temperature.<br>**Disadvantages:** Glucose readings vary in individuals; requires additional calibration for differences in skin and underlying tissues among individuals; difficulty in calibration; Pendra tape needs to be changed every 24 h; device needs to be reattached at the same spot where it was calibrated followed by 1-hour equilibrium time; poor correlation of only 35 % with glucose meters; Clark Error Grid Analysis indicated 4.3 % readings in error zone E; patient must rest for 60 min for equilibration before the reading; it cannot be used in many subjects whose skin types and basic skin impedances are unsuitable for the device; poor accuracy in post-marketing validation study |
| Ultrasound, electromagnetic and heat capacity | Integrity Applications Ltd | GlucoTrack™ | Ear lobe skin | **Advantages:** High precision and accuracy as it employs various NI-CGM techniques; easy calibration procedure; calibration is valid for one month; USB and IR connectivity, alerts for hypo- and hyperglycemia, multi-user support, data-storage capacity, and software for data analysis; readings were unaffected by daily routine activities; high accuracy in clinical trials; good correlation with glucose meters and glucose analyzers; compact and lightweight device with large LCD screen<br>**Disadvantages:** Requires individual calibration against invasive basal and post-prandial blood glucose references before it can be used for glucose measurements; needs improvements in calibration procedure and algorithm for data processing |
| Occlusion NIR spectroscopy | OrSense Ltd | OrSense NBM-200G | Fingertip skin | **Advantages:** CE approved; allows noninvasive measurement of glucose as well as hemoglobin and oxygen saturation; portable, easy-to-use and measures glucose in less than a minute; data-storage capacity, alarm alerts, trend data analysis and integrated wireless telemetry; does not require frequent calibrations; easy calibration procedure; measures glucose continuously for 24 h; good accuracy in clinical trials that was similar to glucose meters<br>**Disadvantages:** Not mentioned |
| Laser microporation | SpectRx Inc. (Guided Therapeutics, Inc.) | | Skin | **Advantages:** Glucose measurements in the interstitial fluid by this device correlated well with those by commercial analyzer and glucose meters; easy calibration procedure; wireless telemetry<br>**Disadvantages:** Requires calibration with a blood glucose meter; glucose measurements in interstitial fluid have time lag of 2–4 min with respect to blood |
| Prelude® SkinPrep System | Echo Therapeutics, Inc. (Sontra Medical Corporation) | Symphony™ | Skin | **Advantages:** Brief warm-up period; glucose measurement every minute; wireless telemetry; alarm alerts for rapid changes in glucose concentration; no skin irritation; highly successful clinical trials; good correlation with glucose analyzers and glucose meters<br>**Disadvantages:** Not mentioned |

## Table 1: Continued

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| B) Systems lacking well-documented clinical trials: | | | | |
| NIR spectroscopy | Biocontrol Technology, Inc. | Diasensor© | Forearm skin | Large size and could not detect hypoglycemic events |
| Photoacoustic spectroscopy | Glucon Medical Ltd | Aprise© | Forearm skin | Compact, lightweight, and measures glucose every 3 seconds inside the blood vessels with high specificity and sensitivity |
| Impedence spectroscopy | Calisto Medical, Inc. | Glucoband© | Wrist skin | Data transfer via USB; data-storage capacity; long-lasting batteries; rapid self-calibration before each measurement; alerts for hypo- and hyperglycemia; no disposable waste |
| NIR spectroscopy | LifeTrac Systems Inc. | SugarTrac™ | Skin | Blood-glucose measurement in less than a minute; safe for patient as device components do not touch the skin |
| NIR spectroscopy | Futrex medical Instrumentation, Inc. | Dream Beam | Fingertip skin | Portable, compact, and battery-powered but requires individual calibration |
| Reverse iontophoresis | KMH Co. Ltd | GluCall | Skin | Korean FDA approved; alarm alerts for hypo- and hyperglycemia; data-storage capacity; PC connectivity and software-based analysis; but requires warm-up period of 1 hour before measurement and calibration with blood glucose meter after measurement |
| Elecromagnetic sensing | ArithMed GmbH and Samsung Fine Chemicals Co. Ltd | GluControl GC300® | Fingertip skin | Portable, battery-powered, and data-storage capacity |
| Thermal spectroscopy | Hitachi Ltd | | Fingertip skin | Compact device with integrated sensors to detect physiologic parameters |
| Novel fluid extraction technology | University of Missouri-St Louis | | Skin | Compact device with novel fluid-extraction technology to provide stable interstitial fluid samples |
| Electromagnetic sensing | University of Missouri-St Louis | TouchTrak Pro 200 | Fingertip skin | Portable device with high cost |
| Optical coherence tomography | University of Missouri-St Louis | | Skin | Portable |
| Fluorescence technology | University of Missouri-St Louis | | Intra-vascular | Employs GluGlow technology based on a glucose-sensing polymer that glows in the presence of glucose |
| Thermal emission spectroscopy | University of Missouri-St Louis | | Tympanic membrane | Portable handheld device that determines blood glucose level in 10 seconds |
| Raman spectroscopy | University of Missouri-St Louis | | FIngertip skin | Portable; employs proprietary tissue modulation process for blood-glucose measurements. |
| NIR spectroscopy | University of Missouri-St Louis | | Skin | Portable; employs proprietary ReSense technology based on the reflection of NIR light from the skin surface |
| Raman spectroscopy | University of Missouri-St Louis | | Skin | Compact, wearable, and water-resistant; glucose measurement in 3 minutes; accuracy similar to currently available continuous glucose monitoring systems; less-expensive glucose determination than glucose meters based on three finger-stick tests per day over 4 years. Clinical studies and trials are needed to validate the results; CE Mark regulatory approval is still pending |
| Raman spectroscopy | University of Missouri-St Louis | | Finger or arm skin | Portable; measures interstitial fluid glucose; use an algorithm to determine the blood glucose level from the glucose concentration in interstitial fluid; uses a DCC-based calibration procedure for precise blood glucose measurements. Clinical studies are required to validate the system; tremendous efforts are still needed to develop a miniaturized device prototype |
| NIR spectroscopy | University of Missouri-St Louis | | | Portable device prototype that detects blood glucose in the capillaries of finger with high precision in just 1 second. Clinical testing and regulatory approvals are required |

*DCC = dynamic concentration correction; FDA = US Food and Drug Administration; NI-CGM = noninvasive continuous glucose monitoring; NIR = near-infrared.*

to begin CGM and frequency of CGM use. Since clinical studies have shown a linear relationship between increased use of CGM and lowered HbA1c, lack of adoption and infrequent use are of significant concern and have spurred the necessity to develop less-invasive technology.

## Minimally Invasive Continuous Glucose Monitoring

Minimally invasive technology has been investigated in the past. The GlucoWatch was a near-continuous RT-CGM device shaped like a watch with hypo- and hyperglycemia alerts. The glucose level was measured and displayed every 10 minutes for up to 13 hours.[19] This technology seemed very appealing as there was no transdermal pricking. However, drawbacks were related to time lag between values, a cumbersome calibration procedure, and poor accuracy in hypoglycemic range. This device has therefore been removed from the market because of the development of more satisfying diabetes-management devices.[20]

Minimally invasive technology attempts to measure glucose concentration avoiding the continuous presence of a foreign object in the body. This is performed by measuring glucose from fluids (interstitial fluid or blood) obtained from the skin tissue. In this case both the sensor and controller are located outside the body and are connected to a fluid-drawing deice that is externally located.

Methods of such monitoring include iontophoresis, sonophoresis, micropore technology, microneedle technology, and skin blister technique. Iontophoresis employs a low electrical current applied across the skin. This current induces a minute amount of interstitial fluid to be withdrawn and sampled by externally locate sensor. Sonophoresis is performed by using low-frequency ultrasound to increase skin permeability which in turn allows interstitial fluid extraction. The skin blister technique employs a minute local epidermal vacuum that creates an interstial fluid-filled blister from which glucose can be measured. Micropore technology creates multiple micropores in the stratum corneum by laser ablation through which interstitial fluid may be collected by application of a small vacuum. Microneedle technology is based on the disposable device use comprising a silicon microneedle and pouch that collects a minute blood sample.[17]

## Noninvasive Continuous Glucose Monitoring

There is a need to minimize discomfort and the potential risk for infection from fluid-withdrawing probes penetrating the skin along with avoiding the foreign body response that otherwise can compromise accuracy. The lack of invasiveness would allow greater tolerability and wearability, therefore increasing sensor adoption rate and long-term adherence. This would ultimately favor reduction in HbA1c and glucose variability and consequently a significant decrease in diabetes acute and chronic complications.

Noninvasive devices include: transdermal sensors that pass near-infrared (NIR) light across the stratum corneum to detect glucose concentrations under optical approaches, and external assays of body fluids (i.e. saliva, tears, breath) using various optical and electrochemical detection methods.

However, current noninvasive technologies have significant drawbacks mainly related to inaccuracies due to variable skin properties: pigmentation, body water content, hydration, nonspecificity to glucose, temperature, poor correlation between blood glucose, and glucose in body fluids (see *Table 1*).[7] Multisensor systems are currently being studied as they may be able to achieve a broader biophysical characterization of the multiple physical and chemical properties of the analyzed tissue — mainly the skin — and improve accuracy under variable conditions.[21]

The development of noninvasive CGM devices faces crucial challenges represented by the improvement of signal-to-noise ratio and sensitivity, development of wearable devices, development of procedures for precise blood glucose determination, and reducing the time taken for glucose measurements. The signal-to-noise ratio and the sensibility of noninvasive CGM devices can be improved by employing next-generation transducers and methods that can perform parallel monitoring of multiple parameters. Retrieved sensor data can be further improved using digital filters and data treatment methods.[7]

## Beyond Hardware

CGM implementation is still suboptimal because of several factors. The first concern is related to the uncertainty of CGM data because glucose readings suffer from interference by noise that confounds their interpretation. Noise may result in false oscillations that could trigger artificial hypo- or hyperglycemic alerts. Some denoising algorithms have been developed to resolve this potentially dangerous phenomenon.[22–24] Another concern is accuracy. CGM data present delays that are mainly secondary to the blood-to-interstitium glucose transport and sensor processing time. Furthermore, systematic under- or overestimations due to calibration problems may add to this inaccuracy.[25] Several strategies have been proposed to compensate the inaccuracy and to enhance CGM data calibration.[26–30] Furthermore, CGM sensors report glucose value with a lag time with respect to blood glucose.

Therefore, there is the necessity of generating predictive hypo- and hyperglycemic alerts by applying short-term glucose prediction algorithms. This would allow the patient to take action before an approaching glucose excursion. Newer insulin pump predictive shutoff algorithms are shown to be able to prevent hypoglycemic events, especially during sleep.[27]

Finally, blood glucose meters are calibrated based on a laboratory reference, but current CGM devices are calibrated against a blood glucose meter, putting them one step behind a laboratory value. To overcome these problems, so-called 'smart CGMs' are being developed reduce uncertainty and inaccuracy of sensor collected data by applying RT algorithms.[23]

## Conclusion

The frequent monitoring of glucose is a fundamental aspect of diabetes management as it is the only way by which blood glucose may be kept within the euglycemic range. Blood glucose meters have already reached an advanced stage in terms of accuracy, cost-effectiveness, convenience, and software-based data analysis and management. In fact, many companies have now started focusing on improving interface, mobile device compatibility, and telemedicine. However, SMBG is still too invasive, time-consuming, and cumbersome to be universally undertaken with sufficient frequency and at the same time be compatible with the daily activities of children and adults alike.[31–33] Poor adherence to glucose monitoring determines an elevated risk for diabetes complications. Continuous and noninvasive technology is therefore warranted. The future of CGM relies not only on advances in hardware technology (lifetime, noninvasiveness, wearability, user interface, lag time, elimination of interference, accuracy, improved calibration, cost-effectiveness, comfort, patient safety), but also by the way the stream of data is processed algorithmically. This will ultimately result in increased accuracy, biocompatibility, and wearability, consequently leading to improved user compliance, health, and quality of life. Furthermore, there still are no universally accepted guidelines regarding how to apply diabetes management decisions using CGM trend information.[34,35]

Although technological improvements are crucial for the success of CGM, one must not forget that any device, no matter how advanced, must be driven and assessed by a human mind. A trained care team and individualized treatment are necessary for effective blood glucose control in each patient. Adequate patient education on CGM data interpretation is fundamental to guarantee a successful outcome. ■

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