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 hypoglycaemia. 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 non-invasive 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.

Blood glucose monitoring is fundamental in the management of diabetes and is essential to optimise glycaemic control. Achieving optimal glucose control is important in reducing the risk of 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 glycaemic 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 recognise 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 hypoglycaemia unawareness (to prevent dangerous episodes of hypoglycaemia).[4,5]

A recent meta-analysis by Langendam et al.[4] shows that there is limited evidence for the effectiveness of real-time CGM (RT-CGM) on glycaemic control. However the reduction in 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 who 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 non-invasive. 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 hypoglycaemic or hyperglycaemic 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 centimetres: one for the CGM and one for the pump. The device presents glucose trend graphs over 3 and 24 hours as well as hypoglycaemic and hyperglycaemic 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 hypoglycaemic or hyperglycaemic 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 (hypoglycaemia) 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 currently 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. Upon 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 tip of the catheter, while the transmitter is located at its other end, which resides outside the skin. Similarly, a disposable, invasive optical fibre 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 hyperglycaemia 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 minimise time spent in hypoglycaemic and hyperglycaemic 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, oedema 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 hyperglycaemia by repeated insulin boluses or overcorrect hypoglycaemia by multiple carbohydrate doses.[14] This may ultimately lead to an increased risk of hypo- and hyperglycaemia. 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 analyse the data, it has been shown to be advantageous to patients by increasing their time spent in euglycaemic range. This can improve the patient's glycaemic 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-/hyperglycaemia, predictive alerts) it has not been embraced. Several reasons such as complexity, inaccuracy, inappropriate expectations, invasiveness, cost, pain, discomfort, risk of infection and interference with daily activities remain significant drawbacks.[18] These matters have hampered motivation 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 hyperglycaemia 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 hypoglycaemic 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 use of disposable devices composed of a silicon microneedle and pouch that collects a minute blood sample.[17]

Non-invasive Continuous Glucose Monitoring

There is a need to minimise discomfort and the potential risk of 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 favour reduction in HbA1c and glucose variability and consequently a significant decrease in diabetes acute and chronic complications.

Non-invasive 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 non-invasive technologies have significant drawbacks mainly related to inaccuracies due to variable skin properties: pigmentation, body water content, hydration, non-specificity 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 characterisation of the multiple physical and chemical properties of the analysed tissue – mainly the skin – and improve accuracy under variable conditions.[21]

The development of non-invasive 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 non-invasive 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 hyperglycaemic 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 hyperglycaemic 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 hypoglycaemic 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 euglycaemic 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 of diabetes complications. Continuous and non-invasive technology is therefore warranted. The future of CGM relies not only on advances in hardware technology (lifetime, non-invasiveness, 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 neglect that any device, no matter how advanced, must be driven and assessed by a human mind. A trained care team and individualised 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. ■

Table 1: Technologies for Non-invasive Diabetes Management[7]

Technology Employed	Company	Device	Target Site	Characteristics
A) Main devices with substantiated claims:				
Reverse iontophoresis	Animas Technologies (Cygnus Inc.)	GlucoW-atch© 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 **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 hypoglycaemia
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 hypoglycaemia; self-correction for changes in impedance due to variations in temperature. **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 hyperglycaemia, 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 analysers; compact and lightweight device with large LCD screen **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 non-invasive measurement of glucose as well as haemoglobin 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 **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 analyser and glucose meters; easy calibration procedure; wireless telemetry. **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 min; wireless telemetry; alarm alerts for rapid changes in glucose concentration; no skin irritation; highly successful clinical trials; good correlation with glucose analysers and glucose meters **Disadvantages:** Not mentioned

Table 1: Continued...

B) Systems lacking well-documented clinical trials:				
NIR spectroscopy	Biocontrol Technology, Inc.	Diasensor©	Forearm skin	Large size and could not detect hypoglycaemic 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 hyperglycaemia; no disposable waste
NIR spectoscopy	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 hyperglycaemia; data-storage capacity; PC connectivity and software-based analysis; but requires warm-up period of one 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 physiological 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 miniaturised 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 = non-invasive continuous glucose monitoring; NIR = near-infrared.

1. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group, *N Engl J Med*, 1993;329:977–86.
2. Boland E, Monsod T, Delucia M, et al., Limitations of conventional methods of self-monitoring of blood glucose: lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes, *Diabetes Care*, 2001;24:1858–62.
3. Brauker J, Continuous glucose sensing: future technology developments, Diabetes Technol Ther, 2009;11(Suppl. 1):S25–36.
4. Langendam M, Luijf YM, Hooft L, et al., Continuous glucose monitoring systems for type 1 diabetes mellitus, *Cochrane Database Syst Rev*, 2012;1:CD008101.
5. Bergenstal RM, Tamborlane WV, Ahmann A, et al., Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes, *N Engl J Med*, 2010;363(4):311–20.
6. Phillip M, Danne T, Shalitin S, et al., Use of continuous glucose monitoring in children and adolescents (*), *Pediatr Diabetes*, 2012;13:215–28.
7. Vashist SK, Non-invasive glucose monitoring technology in diabetes management: a review, *Anal Chim Acta*, 2012;750:16-27.
8. Vaddiraju S, Singh H, Burgess DJ, et al., Enhanced glucose sensor linearity using poly(vinyl alcohol) hydrogels, *J Diabetes Sci Technol*, 2009;3:863–74.
9. Moser EG, Morris AA, Garg SK, Emerging diabetes therapies and technologies, *Diabetes Res Clin Pract*, 2012;97:16–26.
10. Gilliam LK, Hirsch IB, Practical aspects of real-time continuous glucose monitoring, *Diabetes Technol Ther*, 2009;11(Suppl. 1):S75–82.
11. Hirsch IB, Insulin delivery devices – pumps and pens, *Diabetes Technol Ther*, 2010;12(Suppl. 1):S115–16.
12. Garg S, Zisser H, Schwartz S, et al., Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomised controlled trial, *Diabetes Care*, 2006;29:44–50.
13. Garg SK, Potts RO, Ackerman NR, et al., Correlation of fingerstick blood glucose measurements with GlucoWatch biographer glucose results in young subjects with type 1 diabetes, Diabetes Care, 1999;22:1708–14.
14. Ellis SL, Bookout T, Garg SK, Izuora KE, Use of continuous glucose monitoring to improve diabetes mellitus management, *Endocrinol Metab Clin North Am*, 2007;36 Suppl. 2:46–68.
15. Garg SK, Hoff HK, Chase HP, The role of continuous glucose sensors in diabetes care, *Endocrinol Metab Clin North Am*, 2004;33:163–73, x–xi.
16. Rodbard D, Bailey T, Jovanovic L, Improved quality of glycemic control and reduced glycemic variability with use of continuous glucose monitoring, *Diabetes Technol Ther*, 2009;11:717–23.
17. Vaddiraju S, Burgess DJ, Tomazos I, Technologies for continuous glucose monitoring: current problems and future promises, *J Diabetes Sci Technol*, 2010;4:1540–62.
18. Diabetes Research in Children Network Study Group, Weinzimer S, Xing D, et al., Prolonged use of continuous glucose monitors in children with type 1 diabetes on continuous subcutaneous insulin infusion or intensive multiple-daily injection therapy, *Pediatr Diabetes*, 2009;10(2):91–6.
19. Tierney MJ, Tamada JA, Potts RO, et al., The GlucoWatch biographer: a frequent automatic and noninvasive glucose monitor, *Ann Med*, 2000;32(9):632–41.
20. Girardin CM, Huot C, Gonthier M, Delvin E, Continuous glucose monitoring: a review of biochemical perspectives and clinical use in type 1 diabetes, *Clin Biochem*, 2009;42(3):136–42.
21. Zanon M, Sparacino G, Facchinetti A, et al., Non-invasive continuous glucose monitoring: improved accuracy of point and trend estimates of the Multisensor system, *Med Biol Eng Comput*, 2012;50(10):1047–57.
22. Chase JG, Hann CE, Jackson M, et al., Integral-based filtering of continuous glucose sensor measurements for glycaemic control in critical care, *Comput Methods Programs Biomed*, 2006;82(3):238-247.
23. Facchinetti A, Sparacino G, Guerra S, et al., Real-Time Improvement of Continuous Glucose-Monitoring Accuracy: The smart sensor concept, *Diabetes Care*, 2012 (Epub ahead of print).
24. Zecchin C, Facchinetti A, Sparacino G, Cobelli C, et al., Reduction of Number and Duration of Hypoglycemic Events by Glucose Prediction Methods: A Proof-of-Concept In Silico Study, *Diabetes Technol Ther*, 2013;15(1):66–77.
25. Rossetti P, Bondia J, Vehí J, Fanelli CG, Estimating plasma glucose from interstitial glucose: the issue of calibration algorithms in commercial continuous glucose monitoring devices, *Sensors (Basel)*, 2010;10(12):10936–952.
26. King C, Anderson SM, Breton M, Modeling of Calibration Effectiveness and Blood-to-Interstitial Glucose Dynamics as Potential Confounders of the Accuracy of Continuous Glucose Sensors during Hyperinsulinemic Clamp, *J Diabetes Sci Technol*, 2007;1(3):317–22.
27. Guerra S, Facchinetti A, Sparacino G, et al., Enhancing the accuracy of subcutaneous glucose sensors: a real-time deconvolution-based approach, *IEEE Trans Biomed Eng*, 2012;59(6):1658–69.
28. Barceló-Rico F, Bondia J, Díez JL, Rossetti P, A multiple local models approach to accuracy improvement in continuous glucose monitoring, *Diabetes Technol Ther*, 2012;14(1):74–82.
29. Facchinetti A, Sparacino G, Cobelli C, Enhanced accuracy of continuous glucose monitoring by online extended kalman filtering, *Diabetes Technol Ther*, 2010;12(5):353–63.
30. Cameron F, Wilson DM, Buckingham BA, et al., Inpatient studies of a Kalman-filter-based predictive pump shutoff algorithm, *J Diabetes Sci Technol*, 2012;6(5):1142–7.
31. Harris MI, Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes, *Diabetes Care*, 2001;24(6):979–82.
32. Karter AJ, Ferrara A, Darbinian JA, Self-monitoring of blood glucose: language and financial barriers in a managed care population with diabetes, *Diabetes Care*, 2000;23(4):477–83.
33. Vincze G, Barner JC, Lopez D, Factors associated with adherence to self-monitoring of blood glucose among persons with diabetes, Diabetes Educ, 2004;30(1):112–25.
34. Diabetes Research In Children Network (DirecNet) Study Group, Buckingham B, Xing D, Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator), Pediatr Diabetes, 2008;9(2):142–7.
35. Jenkins AJ, Krishnamurthy B, Best JD, et al., Evaluation of an algorithm to guide patients with type 1 diabetes treated with continuous subcutaneous insulin infusion on how to respond to real-time continuous glucose levels: a randomised controlled trial, *Diabetes Care*, 2010;33(6):1242–8.