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REVIEW ARTICLE

Sensors for glucose monitoring: technical and clinical aspects

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Summary

The aim of this article is to critically discuss the technical and clinical aspects of glucose sensors and to briefly review current technical developments. This includes sensors for spot glucose measurements as well as those used for continuous glucose monitoring. Continuous glucose monitoring in particular should supply the diabetic patient with all the information required to optimize insulin therapy and metabolic control. Such systems should also allow hypo- and hyperglycemic episodes to be avoided.

During the last 30 years numerous attempts have been made to develop glucose sensors and new major breakthroughs have been announced repeatedly. However, up until now no glucose sensor has been available that can be used by diabetic patients in daily life conditions. Also one type of glucose sensor, a glucose electrode, recently received approval by the Food and Drug Administration (USA) and is commercially available. Other glucose sensors employing the transdermal, microdialysis or open tissue microperfusion technique are currently under clinical development and may also become available in the near future. The types of glucose sensors referred to so far are not truly non-invasive, but only minimally invasive. They measure glucose concentrations in the interstitial fluid of the skin or the subcutis. Non-invasive optical glucose sensors are designed to monitor glucose changes in the skin by directing light through it. They measure the characteristics of the reflected light that are changed as the result of an interaction with glucose. However, none of the attempts with optical glucose sensors have resulted thus far in the development of a sensor that allows monitoring of glucose with sufficient accuracy and precision within the clinically relevant glucose range in daily life conditions. Nevertheless, more minimal-invasive glucose sensors systems will become available for practical use in the near future, whereas it is still uncertain if this can be said for any non-invasive glucose sensor. Copyright © 2001 John Wiley & Sons, Ltd.

Keywords: glucose monitoring; glucose sensor; glucose electrode; microdialysis; open flow microperfusion

Introduction

During the last 30 years boastful announcements have been made on a regular basis that a sensor for (continuous) glucose monitoring has been nearly completely developed. Now for the first time a practical, usable glucose sensor is available. A glucose electrode (EGMS; MiniMed, Sylmar, CA, USA) has recently been approved for use in diabetic patients in the US and Europe [1]. Also, one type of optical glucose sensor system (Diascensor 2000; Biocontrol Technology, Pittsburgh, PA, USA) is for sale in Europe, but not in the US. However, this first commercially available glucose electrode

does not immediately provide the diabetic patient with the result of the actual glucose measurements. Instead this so-called 'Professional System' collects the data over a period of up to 3 days. The glucose profiles obtained then can only be inspected retrospectively and discussed with the physician. Despite its obvious advantages we do not regard such a system as being sufficient to meet the diabetic patient's daily needs.

There are a number of reviews on the technical properties of the currently available glucose sensors [2–6]. However, the focus of such reviews is on special glucose sensor techniques. Despite the considerable number of such publications, there is still a dearth of data on the clinical use of glucose sensors from a clinical point of view. For example, the fact that a description of their reliability under daily life conditions is still lacking is a problem.

From the diabetic patient's point of view, very little has happened over the last few decades with respect to actual self-monitoring of blood glucose. From the patient's perspective the following aspects are the most relevant:

- replacement of the invasive spot blood glucose measurement
- motivation for additional measurements at special time points, e.g. 90–120 min postprandially and
- upgrading from spot to continuous glucose monitoring.

Continuous glucose monitoring would for the first time provide diabetic patients with a complete picture of blood glucose fluctuations throughout the day. This would provide the patients with the information required to optimize insulin therapy and metabolic control, which is known to drastically reduce the risk of chronic complications [7,8]. At the same time, such a system could provide reliable warning signals of hypo- and hyperglycemic glucose values in order to avoid acute metabolic deterioration over time.

Continuous glucose monitoring also offers new options for the physician to:

- establish at the start of any insulin therapy an individualized treatment schedule under outpatient conditions thus avoiding metabolic ward artifacts and the related additional costs
- keep blood glucose levels prior to and during pregnancy and during intensified insulin therapy continuously within predefined limits without hypoglycemic events
- teach patients and their partners about detailed glucose profiles in vivo and to train them accordingly in more appropriate treatment adjustments than has previously been possible
- optimize metabolic control during clinical emergencies such as surgical procedures, intensive care unit or dialysis treatment
- improve diagnostic procedures of hypoglycemic states unrelated to diabetes mellitus, e.g. insulinoma, of gastrointestinal diseases with malabsorption of carbohydrates or of gestational diabetes and
- provide new insights into blood and tissue glucose excursions during pre-diabetic metabolic conditions associated with e.g. impaired glucose tolerance or impaired fasting glucose.

From the physician's perspective additional aspects of glucose sensors are clinically relevant that are related:

- to the patient's motivation for daily self-monitoring of blood glucose
- to attract additional patients who have been reluctant to control their blood glucose levels sufficiently and
- to the translation of continuous glucose information into treatment decisions.

The aim of the present review is to highlight the general technical and clinical aspects of sensors for glucose monitoring. We only briefly go on to describe the basic principals of the different glucose sensors and critically comment on the sensors that have been examined in clinical trials.

Technical aspects

Minimal-invasive and non-invasive methods

Two different types of glucose sensor need to be distinguished: the minimal-invasive and the non-invasive (Table 1). Minimal-invasive methods measure the glucose concentration in the interstitial fluid of the skin or in the subcutis. The sensor has either to be placed in the tissue to be exposed to interstitial fluid, or the fluid (or an extract of it) has to be transferred outside the body. The advantage of this approach is that glucose can be measured specifically and in absolute concentrations.

Most non-invasive approaches are carried out using optical glucose sensors. The basic premise of optical glucose sensors is to direct a light beam through intact skin and to measure the properties of the reflected light that are altered (1) as result of direct interaction with glucose (spectroscopic approaches) or (2) due to the indirect effects of glucose by inducing changes in the physical properties of the skin (scattering approach). The major problem with non-invasive optical sensors is the measurement of glucose specifically with sufficient precision. For more detailed information, different sensor types and the internet addresses of related companies are summarized in Table 2.

Relationship between glucose levels in blood and interstitial fluid

Self-monitoring of metabolic control has to date relied on blood glucose levels. Due to the obvious risks related to

Table 1. Comparison of the properties of minimal-invasive and non-invasive glucose sensors

Properties	Glucose electrodes	Microdialysis	Microperfusion	Transdermal approaches	Optical sensor spectroscopy	Optical sensor scanning
Invasive	Yes	Yes	Yes	No (?)	No	No
Long-term stability	No	Yes	Yes	No (?)	No	No (?)
Continuous measurement	Yes	Yes	Yes	Yes/No	No (?)	Yes
Clinical results	Yes	Yes	No	Yes	No	No
For sale	Yes	Yes/No	No	Yes	Yes/No	No

inserting a glucose sensor in the intravasal compartment for longer periods of time, sensors are placed in extravascular compartments or externally (Fig. 1). Consequently glucose sensors do not measure blood glucose *per se* but glucose concentration in other compartments. Minimal-invasive sensors measure glucose levels in the interstitial fluid, whereas non-invasive sensors measure a composite of glucose levels in the intracellular, interstitial and intravascular compartments.

In human skin, a prominent volume fraction of the tissue is interstitial fluid (~45%), whereas blood vessels represent only ~5% of the tissue volume [4]. Thus the glucose changes in skin tissue are only to a small degree related to the changes in blood glucose. In the subcutaneous tissue, the proportion of interstitial fluid is lower than in the skin and is variable, depending on the size of the adipocytes. This also has an impact on adipose tissue blood flow, i.e. it is reduced in obese subjects [9].

Under physiological conditions there is a free and rapid exchange of glucose molecules between blood plasma and interstitial fluid and, for this reason, changes in blood glucose and interstitial glucose are strongly correlated [4,10]. Nevertheless, changes of glucose levels in interstitial fluid do not occur at the same time as those in the intravasal compartment; they occur with a delay. This physiological lag time is reported to vary between a few seconds and 15 min [4,11]. The magnitude of the delay may vary depending on the absolute glucose levels and the rate and direction of change. This physiological delay complicates the interpretation of measurement results and can be dangerous, e.g. if blood glucose levels decline more rapidly than interstitial ones to hypoglycemic values. In addition, in diabetic patients the altered capillary wall structure may increase the diffusion barrier and thereby prolong the physiological lag time. Also, the intra- and inter-individual variability of the delay between glucose changes in blood and in interstitial fluid remains to be clarified.

Absolute glucose concentrations of interstitial fluid in comparison with blood are also a matter of debate: are the glucose levels identical in both compartments? Most studies performed so far investigated this relationship under steady-state conditions. Depending on the technique used, the reported values for interstitial glucose levels vary between 50 and 100% of the intravasal value [4].

Table 2. Sensor types and internet addresses of related companies

Sensor type	Company	URL
Glucose electrode	MiniMed	www.minimed.com/files/cgms/cgms_web.htm
Microdialysis	CMA	www.microdialysis.se
Microdialysis	Menarini	www.menarini.com
Microdialysis	Roche Diagnostics	www.roche.de/index.htm
Microdialysis	Disetronic	www.disetronic.com
Open flow microperfusion	Disetronic	www.eticalo.org
Transdermal glucose sensor	Bioject	www.bioject.com
Transdermal glucose sensor	Cygnus	www.cygn.com/glucowatch.html
Transdermal glucose sensor	K-2	www.glucose-monitor.com
Transdermal glucose sensor	Intelli	www.intelliquine.com
Transdermal glucose sensor	Kumetrix	www.kumetrix.com/technology.html
Transdermal glucose sensor	SpectRx (Abbott)	www.spectrx.com/flow/glucose.html
Transdermal glucose sensor	ICU	www.tecdiben.com/noninvasi.html
Non-invasive optical glucose sensor	AdMed	www.admed.de/home.htm
Non-invasive optical glucose sensor	Biocontrol Technology	www.bicn.com/dl000g.htm
Non-invasive optical glucose sensor	CMA Telemetric	www.cmetele.com/diabetes.asp
Non-invasive optical glucose sensor	Futrex	www.futrex.com/guc/ne.html
Non-invasive optical glucose sensor	Instrumentation Metrics	www.instrumentation-metrics.com
Non-invasive optical glucose sensor	Light Touch	www.lightouchmedical.com/pt.html
Non-invasive optical glucose sensor	International Diagnostics Technologies	www.abcbiosa.com
Non-invasive optical glucose sensor	O-Sense	www.o-sense.com/mid.html
Non-invasive optical glucose sensor	Sentec	www.sentec.com/blood/glucose_technology.html
Non-invasive magnetic resonance technology	Magnetic Diagnostics	www.mdhome.com
Implantable optical glucose sensor	Animas	www.animascorp.com/sensor.html
Implantable sensors with different measurement technologies	Sensile Biotech	www.sensile.ch/de/projekte/index.html

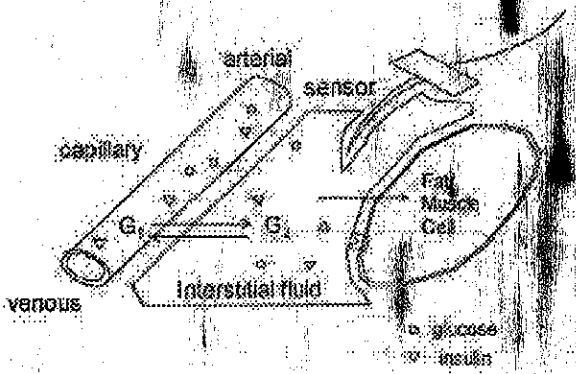

Figure 1. Glucose electrode inserted in subcutaneous tissue. Glucose diffuses from the intravasal compartment (G_1) into the interstitial compartment (G_2) and is then taken up by cells if insulin is present (modified after [11]).

One explanation for such a difference is that glucose levels in the interstitial fluid (and also in venous blood) differ between body regions depending on local factors that influence interstitial glucose clearance. Obviously, studies still need to be done to investigate the relationship between glucose levels in blood and interstitial fluid under non-steady-state conditions, e.g. during exercise or postprandially.

Conditions of measurement

Physiologically, the human body monitors glycemic changes continuously, i.e. with a delay in the range of seconds, and glucose is transported from the blood to islet cells in the pancreas via the interstitial fluid surrounding the cells. This immediately leads to subsequent islet cell responses. The duration of the measurement is not only short and the measurement system is permanently active, also the induced metabolic reaction occurs without a delay. This response not only depends on the absolute magnitude of the glucose level, but also on the rate of change. Thus, the human body makes use of trend information in addition to absolute glucose levels.

Assuming that such a behavior is the best way to achieve optimal metabolic control, the following requirements need to be met by glucose sensors:

1. *Immediate availability of the measurement result.* There are two different reasons for delayed availability.
   (1) A physical time lag. This is the time required to collect and/or transfer a sample, e.g. from the interstitial fluid via the dialysis catheter to the glucose electrode outside the body. In this case, up to 30 min must be added to the physiological lag time.
   (2) The time required for signal analysis. With optical glucose sensors, the complex analysis procedures of the measured signals can take several hours. The use of optimized algorithms and specially designed computers should reduce the time required considerably.
2. *High frequency of measurements.* In which intervals should glucose measurements be performed in order to monitor clinically relevant glucose changes adequately? Ideal monitoring should be continuous. From the clinical perspective the most critical aspect is a rapid decline in blood glucose (2–3 mg/dl/min) into the hypoglycemic range. At least a decline of 10 mg/dl in 5 min must be detected. Thus, it is questionable if measurement intervals > 5 min would be sufficient.
3. *Fast sensor signal stability after application.* As with all types of glucose sensors after application, a certain time is required before the sensor signal is stable, on account of the equilibration process between the analyte and the sensor surface. Because of this phenomenon, no measurement is possible with a transdermal sensor system (GlucoWatch, see later) within the first 3 h following application. Defining the duration of the so-called 'run-in period' is difficult *in vivo*. It seems to vary not only between the different sensor types, but also shows a high intra- and inter-individual variability with one type of sensor.
4. *Sensor signal stability over time.* Some types of glucose sensors exhibit a 'drift' in their sensor signal when applied *in vivo*. Various reasons may be responsible for the drift. In the case of glucose electrodes, the surface of the electrode is covered with cells and other substances as the result of a foreign body reaction. In the case of optical glucose sensors, interaction of the sensor bead with the skin can lead to sensor signal drift. Such a drift can result in a complete loss of correlation between changes in the sensor signal and glucose levels. Compensation of drift is possible at least for a limited time by re-calibration.

Calibration

Up until now, the adjustment of diabetes therapy in relation to metabolic control has been based on blood glucose measurements [7,8]. However interstitial glucose levels are more closely related to metabolic changes in muscle cells, fat cells, and cells in other tissues compared to intravasal levels. Unfortunately, the relevance of interstitial glucose levels for diabetes-related endpoints has not been studied to date. In other words, for historical reasons physicians and patients make therapeutic decisions on the basis of blood glucose values, whereas most probably interstitial glucose levels are of greater relevance to therapeutic decisions and diabetic late complications.

Usually sensor signals are transformed by means of a calibration process with the intention of matching actual blood glucose levels and not the interstitial glucose levels. During such a process, blood glucose is measured by a conventional capillary measurement and then related to the glucose sensor signal measured at the same time. All subsequent glucose sensor values are then adjusted

accordingly. Should the calibration factor be inaccurately estimated, this error would perpetuate with potentially serious clinical implications.

Whether such a primary calibration process can be based on one blood glucose level ('one-point calibration') or if measurements at two glycemic levels ('two-point calibration') are mandatory remains to be clarified. Another question is: how often has the sensor signal to be re-calibrated per day after the primary calibration? Presently, at least one re-calibration per day is recommended. Thus the introduction of glucose sensors will not make conventional blood glucose measurements obsolete.

A profound drift of the sensor signal over time due to a foreign body reaction might limit the number of re-calibrations. For example, glucose electrodes show a considerable signal drift within 3 days. This is one of the reasons why MiniMed limits the use of their marketed glucose electrode for this time period. Other reasons for signal drift might be varying temperatures or altitudes that make additional re-calibration necessary.

Duration of sensor application

The main disadvantage of minimally invasive glucose sensors is the necessity to break the skin barrier. Penetration of the skin always carries the risk of local infection, inflammatory response, and inflammatory reaction against the artificial material inserted. This limits the length of time the sensor can stay in place to a number of days. The mechanisms used by transdermal glucose sensors to drag interstitial fluid across the skin induces skin irritations which can persist for up to several days. Non-invasive glucose sensors that do not penetrate the skin but occlude a given skin area for prolonged periods of time also induce local skin irritation. Therefore such sensors have to be attached to a different skin location each time. Thus none of the glucose sensors under development can remain in place for prolonged periods of time.

Depending on the type of glucose sensor and the measurement system that is combined with the sensor, technical factors (e.g. energy supply, waste handling, data storage) may also limit the duration of application.

Quality control

With conventional blood glucose meters, usually a certain level of quality control of the measurement properties is available. It would be reasonable to apply at least a comparable quality control system to glucose sensors. The plausibility of the actual glucose measurement should also automatically be checked by the glucose sensor system: is the value in accordance with previous values, is it within certain limits, and so on?

Minimal-invasive glucose sensors

Transdermal approaches

Different techniques are currently under development which try to avoid penetration of the skin in order to gain access to interstitial fluid [3]. The idea is to attach a device to the skin that removes interstitial intradermal fluid across the skin, assuming blood glucose to be in equilibrium with extracellular fluid.

The basic principle of the GlucoWatch Biographer (GlucoWatch; Cygnus, Redwood City, CA, USA) is to apply a low current to the skin in order to drag ions through the skin ('reverse iontophoresis') [12–14]. Thereby interstitial fluid is also extracted across the skin. Together with the fluid, small amounts of glucose (about 1/1000 of those in blood) are transferred. The glucose oxidase reaction used to measure glucose must be pushed to its limits to allow a precise and accurate measurement. Following a 3-h warm-up period, the device is capable of providing up to three glucose readings per hour for 12 h after a single-point calibration with a conventional self-blood glucose measurement. In a series of feasibility studies, the accuracy and precision of the measurements were evaluated in comparison with established methods. The unit gives acceptable results from 40 to 400 mg/dl. The current applied to the skin causes some degree of local skin irritation that was regarded to be mild or moderate during the feasibility studies in most cases. The irritation is claimed to clear within 3–27 days. The device cannot be used during periods of increased sweating.

Other companies have also developed transdermal glucose monitoring devices. SpectRx (Norcross, GA, USA) developed a system that can continuously drag dermal interstitial fluid over a period of some days through a number of small holes ('micropores') that are burnt into the outer layers of the skin by means of a laser beam. TCPL (Fort Lauderdale, FL, USA) has a 'patch' with a transdermal permeation enhancer that is placed on the forearm for 5 min, after which time a meter is placed in the tabbed area of the patch to take the spot glucose reading [15].

It remains to be established whether in the long run the skin tolerates the principles used in transdermal glucose sensors. Another problem is a considerable time lag due to the time needed for the transfer of interstitial fluid across the skin [12].

Other novel transdermal approaches use fluorescent molecules [6] or low-frequency ultrasound [16]. Covalent binding of a fluorescent dye to glucose reduces its fluorescence intensity when excited appropriately. Application of ultrasound to the skin induces an increase in skin permeability resulting in an increased transdermal glucose flux if extracted in an appropriate manner.

Glucose electrodes

Thin glucose electrodes were the first to be inserted into the skin [17]. The basic principle employed with most of these electrodes is to immobilize the glucose-specific enzyme, glucose oxidase, on the tip of a needle that is constructed of two different metals with an insulating material between them. This allows application of a potential to sustain. Such 'amperometric enzyme electrodes' monitor glucose in interstitial fluid by measuring the change in current flow caused by the enzyme-catalyzed production of hydrogen peroxide. *In vitro* and animal experiments were so promising that in the beginning it was believed that these glucose electrodes would soon become available. However, it transpired that the long-term stability of the sensor signal is insufficient [18]. The main problem is the lack of biocompatibility of the electrode surface. Due to a foreign body reaction, coating of the electrode surface occurred that led to a rapid decline in the sensor signal.

The glucose electrode developed by the MiniMed Company also shows a drift of the sensor signal over time [11]. Nevertheless, this problem – at least partially – can be overcome by repeated re-calibration which requires blood glucose measurements at least once per day. The needle-like glucose sensor of this system is inserted into the abdominal skin. The monitor reads glucose values every 5 min for a time period of up to 72 h. The first generation of the glucose sensor marketed by MiniMed does not display the current glucose concentration measured, but stores the data for up to 3 days ('Professional System'). Thereafter the physician has to read out the retrospectively calibrated data and discuss them with the patient. Clinical trials with several hundred thousands of glucose readings showed a close agreement with capillary glucose readings over the 40–400 mg/dl range [1].

Recently a glucose sensor developed by the Medical Research Group (Sylmar, CA, USA) was successfully implanted for 14 days into patients with type 1 diabetes *via* subclavian vein catheterization [19]. The sensor portion of the catheter-based device was positioned into the superior vena cava and the sensor output was recorded every minute showing close agreement with parallel blood glucose readings over the range 36–400 mg/dl. No sensor re-calibration was necessary.

Microdialysis

Microdialysis imitates the function of capillaries. By inserting a semi-permeable dialysis fibre into the subcutaneous tissue and perfusing the fibre with isotonic glucose-free fluid, a dialysate of the interstitial fluid can be collected. Due to the concentration gradient, glucose diffuses from the interstitial fluid through the dialysis membrane into the perfusate. The dialysate is pumped to a glucose sensor outside the body where the glucose concentration is measured continuously [9,20–25].

An advantage of this approach is that a foreign body reaction is avoided, which allows continuous monitoring without profound signal drift. A disadvantage is the physical time lag inherent to this technique which can vary between 5 and 45 min [9]. This delay is due to the length plus the inner diameter of the tubing and the perfusion flow rate selected (between 0.1 and 10 µl/min). Also with this method re-calibration is required at least a once daily.

Over the last few years clinical studies have been performed with this technique showing that it allows glycemic changes to be monitored continuously over prolonged periods of time [26–28]. A microdialysis system that allows semi-continuous glucose monitoring under hospital conditions is available (CMA Microdialysis, Solna, Sweden). Roche Diagnostics (Mannheim, Germany) has recently developed a new microdialysis system for daily life conditions that registers continuously over 72 h. The Menarini company (Florence, Italy) had also developed a microdialysis system which recently has been certified for 24-h use [29].

Open-flow microperfusion

For open-flow microperfusion a double-lumen catheter with microholes must be inserted into the subcutaneous adipose tissue [30,31]. A sterile, ion-free isotonic perfusion fluid is then continuously pumped through the inner cannula. The perfusion fluid emerges at the tip of the probe, mixes itself with the interstitial fluid, and this mixture is sucked back through the space between the inner cannula and the perforated outer cannula. Partial equilibrium occurs between the perfusate and the surrounding interstitial fluid. The macroscopic perforations of the catheter permit unrestricted exchange of solutes between the perfusion medium and the interstitial fluid, and thus an open exchange of large and small molecules. In samples of the resulting mixture, glucose and sodium concentrations are measured. The sodium measurement (conductivity) serves as an ionic reference method that describes the degree of mixing that takes place. This technique does not require a calibration process. The interstitial glucose levels measured with this system average 60–70% of those obtained using simultaneous blood glucose readings.

Non-invasive glucose sensors

Optical glucose sensors have to deal with the problem that human skin allows penetration of light up to some centimeters into the skin only in a certain wavelength range (600–1300 nm; the near infrared region). Light

with a wavelength above or below this 'optical window' is absorbed by water, skin pigments or blood within the outer layers of the skin [32]. Hence, only light in the near infrared region can penetrate to the deeper blood-perfused skin layers, potentially allowing glucose monitoring.

Other technologies such as polarimetry, far infrared radiation spectroscopy, radio wave impedance, pulsed photoacoustic, and fluorescence spectroscopy in principle also allow non-invasive glucose monitoring [3,6,33,34]. However, most of these approaches are at the pre-clinical stage and it is not known whether they will allow *in vivo* glucose monitoring with sufficient precision. Therefore they are not discussed further in the present review.

Spectroscopic approaches

Glucose, like any other molecule, shows a typical absorption spectrum when a light beam is directed through a cuvette with a clear solution of glucose in water. This 'fingerprint' of glucose allows quantification of the solute in the laboratory with high precision. Spectrophotometry, used as a method to quantify solutes in liquids, is based on solute-specific absorption bands in the visible, near infrared or mid infrared spectral range. Today the *ex vivo* quantification of glucose in complex matrices such as plasma, serum or whole blood is feasible using this approach [2,5].

It was expected that it would also be possible to use spectrophotometric approaches to measure glucose non-invasively in the human skin. Therefore, measurement of the light absorption properties of human skin is the technique most studied for non-invasive optical glucose sensors. However, despite more than 25 years of intensive research, numerous publications, many patents and the spending of much research funds, no reliable working system has yet been developed. The major challenge is to achieve sufficient precision within the clinically relevant blood glucose range over prolonged periods of time. The non-invasive optical glucose sensor from Bioscanner (Diascanner 2000) does not fulfil these requirements, even though this device is for sale in some countries. The current status of blood glucose monitoring in human skin by near infrared absorption measurements using different spectrophotometric methods has been reviewed recently [2,5,35].

If a good correlation between blood glucose and the results of spectroscopic analysis has been reported by a number of researchers [36–42], why is the long-term accuracy and stability of this approach so disappointing [43]? Various problems are associated with optical spectroscopy, namely: (1) glucose has no specific absorption pattern in the near infrared region, (2) glucose concentration in tissue is low, (3) the absorption signal is massively reduced by light scattering (see later), (4) prominent interfering light absorbers (such as water) in high concentrations are prevailing, (5) light absorption shows a profound temperature dependence, (6) light-absorbing structures are heterogeneously distributed in the skin, and (7) glucose is heterogeneously distributed in different tissue compartments. Therefore, changes in blood glucose induce only very small and unspecific changes in the absorption spectra. It is only with complex mathematical procedures that quantification of glucose in complex matrices such as plasma or whole blood has become feasible *ex vivo*. However, precision of spectroscopic measurements in human skin is insufficient for clinical requirements. Such 'chemometric' methods must be used very carefully, because of the risk of 'overfitting' the data (see later) [44]. These difficulties explain why none of the many attempts to develop optical glucose sensors has been successful thus far.

In contrast to this position are data from a recent study in which the performance of a transcutaneous glucose monitor was evaluated assessing the absorbency spectra in the thumb in the hypoglycemic and euglycemic ranges [40]. The authors conclude that their approach allows accurate prediction of plasma glucose levels in the euglycemic and hypoglycemic ranges. The surprisingly precise measurements reported in this study might be due to the multivariate calibration method employed to analyze the registered spectra [41]. It is well known that chance correlation and overfitting could easily have led to a false positive result.

The use of novel techniques such as pulsatile spectroscopy (e.g. pulse oximetry) may help to overcome some of the problems already described [32]. The idea is to make several spectroscopic measurements per second, allow probing of parts of the intravascular fluid space, as its arterial volume is modulated by the heart beat. Spectrum changes can be monitored synchronously to the cardiac cycle.

Scattering

Next to light absorption, the other major optical interaction mechanism in tissue is light scattering. This is one of the major drawbacks of the spectroscopic approaches. There are many different structures in skin tissue that scatter light, e.g. cell membranes, cell organelles, collagen fibres. It is more likely that a photon in the near infrared range is scattered than absorbed in tissue.

In turbid suspensions (such as human skin) the scattering of light depends on the ratio of the refractive indices of the particles to the solution. Each change in the ratio of the refractive indices of the scattering particles and the solute leads to a variation in the 'transparency' of the tissue. An increase in blood glucose concentration

leads to a subsequent rise in the refractive index of blood and interstitial fluid (the solution), whereas the refractive index of scattering particles in the skin remains unchanged [45,46]. Thus, the ratio is lowered and the scattering is decreased. The proportion of light that is scattered in skin is a little bit lower and subsequently the intensity of light reflected back to the skin is reduced. The dominating light scattering mechanism in tissue is Mie scattering which takes place when the size of the scattering particles and the wavelength of light are of the same order of magnitude.

The feasibility of this concept for continuous and non-invasive glucose monitoring was evaluated first in type 1 diabetic patients [47]. By means of the glucose clamp technique rapid changes in blood glucose from euglycaemic to hyperglycaemic values and back to euglycemic values were induced. This led to a decline in the light scattering coefficient of the skin by approximately 1% per 5.5 mmol/l change in blood glucose. The correlation with blood glucose concentrations was often excellent (above 0.95). These results show that in principle glucose monitoring is possible by measuring the light scattering properties of human skin. The observed sensitivity of the scattering coefficient to glucose changes is small in absolute terms. However, the changes were much higher than those due to glucose-specific light absorption in the near infrared region. Subsequent studies with healthy volunteers and type 2 diabetic patients showed that slower changes in glycemia induced by an oral glucose load (75 g) can also be monitored by measuring the scattering coefficient of the skin in most of the experiments [48].

In contrast to the spectroscopic technique, the scattering approach does not specifically measure glucose, but derives the glucose concentration indirectly from (glucose-induced) changes in refractive indices. Therefore, other blood analytes and physiological factors, such as shifts in the water/plasma distribution between the intravasal and the interstitial compartment, may influence the scattering coefficient. Nevertheless, the accordance of the observed *in vivo* sensitivity of the glucose effect on scattering coefficient with theoretical considerations and experimental *in vitro* results indicate that the variation of the refractive index of body fluids is a predominant factor for glucose-related variations in light scattering of skin tissue.

An advantage of the scattering approach is that no specific absorption bands are needed, which is important for technical realization. With this approach, the 'absolute' scattering coefficient cannot be measured, but relative changes continuously over time can. Due to a considerable local variability of the baseline scattering coefficient, *in vivo* calibration of the scattering signal with respect to the prevailing blood glucose will be necessary at regular intervals.

Clinical aspects

Presentation and interpretation of data: new horizons for patients and physicians

The presentation of the vast amount of data collected during continuous glucose monitoring must be made in such a way that diabetic patients are able to easily understand the data and to interpret them adequately. This might sound trivial. However, many patients are not used to reading and interpreting numbers and graphs in the way that physicians do. There are different ways of presenting glucose sensor data for clinical use as described below.

1. *Actual glucose reading.* The glucose sensor system display should show the result of the actual glucose measurement. A warning signal can be given if the actual glucose value is below or above a pre-selected level. The patient might be advised to confirm this signal with a conventional blood glucose measurement. But the patient (and the diabetologist) must bear in mind that this value reflects the blood glucose concentration some time in the past, depending on the physiological time lag and the physical time lag which is system-specific.
2. *Trend information.* Continuous glucose monitoring provides a new opportunity, namely comparison of the actual measurement result with the results of the last 30 mins. By presenting the direction of glucose changes, this trend analysis can provide the diabetic patient with important additional information in order to take preventive actions in time. It remains to be clarified in detail how many measurements have to be taken into consideration to detect relevant clinical glucose changes. Clearly the most dangerous situation, a rapid decline in blood glucose, must be adequately detected by the trend analysis. A warning signal should be given before the actual value is below a critical value, but when most probably the next values will be. It might also be possible in the future, by means of more complex mathematical trend analysis, to predict the course of glucose changes for longer time periods ahead.
3. *Glucose profile over 24 h.* At present, the limited number of self-measurements made per day does not give an accurate impression of the blood glucose profile over 24 h. Usually postprandial glucose excursions and the probable subsequent decline to low glucose levels, and also the change in blood glucose during the night, are not monitored by blood glucose self-monitoring. A monitoring of glucose changes over 24 h detects much larger glucose fluctuations than usually anticipated [20]. Frequent hypo- and hyperglycemic periods were observed even in patients with glycated haemoglobin <7%. Therefore, glucose sensor systems should provide the opportunity to display all glucose readings

from a single day as a 24-h profile. However, one has to bear in mind the fact that many patients and physicians are not used to interpreting these daily profiles, and are not accustomed to thinking about daily blood glucose patterns. It has taken physicians some time to learn to interpret 24-h blood pressure profiles adequately. Therefore, appropriate teaching and treatment programs have to be implemented (see later).

4. *Glucose profiles over extended periods of time.* Up until now diabetic patients most often document the results of blood glucose self-measurements in a diary. This helps the physician to advise the diabetic patient on his or her diabetes therapy. In the past, several attempts have been made to transfer the results of blood glucose self-measurements from the glucose meter into a computer and to analyze them. Optionally, the profiles of several days should be superimposed to detect time periods with special events (i.e. patterns). Such systems are aimed at helping the patient and the physician interpret data collected over extended periods of time by providing graphical presentations and statistical data. However, in view of the small number of measurements per day available up to now, it is not surprising that the value of such information is only limited. Subsequently, such systems have not gained a wide acceptance.

Continuously working glucose sensors should help to overcome this hurdle. Adequate changes in diabetes therapy can be initiated and their success can be followed directly. One does not have to wait for months until a decline in the glycated hemoglobin or a reduction in the frequency of hypoglycemic events indicate that the therapeutic modifications are adequate. This is a new and important opportunity.

Teaching and treatment programs

Diabetic patients are trained during structured teaching and treatment programs to perform self-monitoring, to interpret the glucose measurement results, and to translate them into sensible therapeutic action. Invention of glucose monitoring with glucose sensors requires new teaching and treatment programs. First of all, adequate training programs for all professionals in the diabetes treatment team are required. Diabetic patients have to learn the proper use of the individual glucose sensor system, which includes calibration and quality control. They must also be instructed on the problems and limitations of each sensor.

Psychological aspects

When patients realize how variable their metabolic control is and how often acute metabolic deteriorations occur, this may come as a shock and may generate fear. This also can lead to a situation in which the patient steadily checks his glucose and tries to counteract every little deviation from the target glucose level. Especially during this phase it is necessary to avoid hysteric reactions due to 'information overload' by an intensive consultation with their physician. An additional problem can be that patients start using a glucose sensor with great enthusiasm and with high expectations, without considering the limitations of the sensor. They might be frustrated if the sensor does not help solve all their problems.

Information about glucose sensors

In the age of the World Wide Web, diabetic patients have immediate access to information provided by the companies developing glucose sensors. Consequently diabetic patients often are better informed about recent developments than are their physicians. Due to the misleading information policy of some companies, diabetic patients can believe that 'ideal' sensors will be available soon. In principle they can buy such glucose sensors by means of a 'mouse click' or 'over the counter' without additional support by the producer and/or distributor.

Concluding comments

Glucose monitoring with a glucose sensor is already possible and more sensors will be available in the next few years. However a number of important questions remain to be studied thoroughly in appropriately designed clinical trials, for example, the intra- and inter-individual variability, precision and accuracy of measurement under all practical circumstances. Clearly, quality and price will decide which product the market will accept. The probably relatively high costs of the individual glucose sensor system have to be seen in the context of (hopefully) optimized metabolic control, which should reduce the cost of treatment of late complications, which clearly outweigh by far the costs of self-monitoring and self-control. Additionally, the cost of metabolic ward treatment of diabetic patients can be reduced, e.g. for optimizing metabolic control, for correcting repeated hypoglycemic events (particularly at night), and for initiating insulin therapy. At present any non-invasive sensor system for glucose monitoring will still require invasive spot blood glucose measurements at least for repeated re-calibrations, verification of e.g. hypoglycemic events, as a reserve method in case of technical failure of the sensor or interruption of its normal function, and so on.

If a glucose sensor becomes available that works with sufficient reliability and precision under daily life conditions, it could be used for building an artificial pancreas, i.e. mimicking the physiological situation [49,50]. With such a machine, the glucose sensor

readings would be immediately transferred to a computer that could calculate the necessary insulin infusion rates by means of appropriate feedback algorithm. This perspective of a 'closed-loop' system is one of the major driving forces for glucose sensor development. The recently developed glucose sensors for use in the superior vena cava have been linked to an implantable infusion system, and a clinical study in French diabetic patients has been initiated to evaluate the clinical feasibility of such a 'closed-loop' system. Implementation of an artificial pancreas should lead to further optimization of metabolic control and would represent a major breakthrough in diabetes therapy. However, safe delivery of insulin in this way requires glucose sensors that have proven their reliability over years of testing [9].

The race to develop glucose sensors continues and has even gained speed while the first sensors are available now.

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