Analytica Chimica Acta 750 (2012) 16–27

Contents lists available at SciVerse ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Review

Non-invasive glucose monitoring technology in diabetes management: A review

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ARTICLE INFO

Article history:
Received 14 January 2012
Received in revised form 23 March 2012
Accepted 23 March 2012
Available online 2 April 2012

Keywords:
Non-invasive
Glucose monitoring
Techniques
Devices
Diabetes

ABSTRACT

The frequent monitoring of glucose is an essential part of diabetes management. Despite the fact that almost all the commercially successful blood glucose monitoring devices are invasive, there is an immense need to develop non-invasive glucose monitoring (NGM) devices that will alleviate the pain and suffering of diabetics associated with the frequent pricking of skin for taking the blood sample for glucose testing. There have been numerous developments in the field of NGM during the last decade, which stress the need for a critical review. This manuscript aims to review the various NGM techniques and devices. The challenges and future trends in NGM are also discussed.

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http://dx.doi.org/10.1016/j.aca.2012.03.043

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Sandeep Kumar Vashist completed his Ph.D. in 2006 from Central Scientific Instruments Organisation, India in the field of BioMEMS based immunodiagnostic kits. He worked as a bioanalytical scientist at Bristol-Myers Squibb Company, Ireland from 2006 to 2009, where he pioneered the development of several technologies in diagnostics and biosensors, and transferred them successfully to the industry. He joined as the Team Leader at NUSNNI-NanoCore, National University of Singapore in 2009 for the development of electrochemical glucose sensors. He has developed several proprietary glucose sensing strategies, filed several patent applications and published extensively in the field of diagnostics and biosensors.

1. Introduction

Diabetes is a serious health concern, which has been declared a global epidemic by World Health Organisation (WHO) due to its rapidly increasing incidence. It is taking a heavy economic toll of US$ 376 billion annually, which will increase to US$ 490 billion in 2030 [1]. The number of diabetics, as estimated by WHO in 2004 [2], was expected to increase from 171 million in 2000 to 366 million by 2030. However, the recent estimates by International Diabetes Federation states 366 million diabetics in 2011 itself and estimated it to increase up to 552 million by 2030 [3,4]. Therefore, diabetes is a potentially serious epidemic that is increasing at an unprecedented pace. It is a major cause of mortality in the age group of 20–79 years. The frequent monitoring of blood glucose is an essential part of diabetic management as only the maintenance of blood glucose level within the physiological range enables a diabetic to lead a healthy lifestyle by avoiding diabetic complications such as diabetic retinopathy, kidney damage, heart diseases, stroke, neuropathy and birth defects. The normal and pathophysiological blood glucose levels are in the range of 4–8 mM (72–144 mg dL^{-1}) and 2–30 mM (36–540 mg dL^{-1}), respectively. The commercial market of blood glucose meters is really substantial i.e. worth US$ 6.1 billion [5], which accounts for 85% of the total biosensors market and is majorly dominated by Roche Diagnostics, Bayer, Abbott, Minimed/Medtronic and LifeScan.

Almost all commercial blood glucose monitoring devices (BGMD) employ a cost-effective electrochemical biosensor, which is capable of being mass produced and responding rapidly to glucose detection. They use automatic lancet devices to prick the fingertip of diabetics for taking the blood sample, which is painful as the diabetic has to measure blood glucose very frequently i.e. more than four times a day. There have been tremendous developments in the last few decades to develop improved BGMD [6] with reduced blood sample requirement of less than 1 μL. The painful aspects are minimized by employing alternate sampling sites (hand, arm), and using 32 gauge lancet. However, the cost of strip and the boredom of making repeated measurements are becoming most important. The minimally invasive approaches have been developed by using subcutaneous sensors to determine glucose concentration in interstitial fluid. But they suffer from limitations in terms of discomfort to patients, requirement of continuous calibration, and high susceptibility to biofouling. Therefore, the development of NGM techniques [7,8] is the only way to develop pain-free glucose monitoring technology for diabetics. This is the major stimulant for continuous ongoing developments in the field of NGM. There have been continuously increasing research efforts in the last few decades as shown by the rapidly increasing number of publications in NGM (Fig. 1). This manuscript provides an update of various potential NGM techniques and devices along with their advantages, limitations, challenges and future trends. Table 1 provides a description of various NGM devices that have been developed till date.

2. Techniques employed for non-invasive glucose monitoring

2.1. Reverse iontophoresis

Iontophoresis has been extensively employed to deliver drugs through the skin by applying an electrical current. On the other hand, reverse iontophoresis [9] transports glucose outward from the skin i.e. in the direction opposite to that of iontophoresis. It involves the application of an electric potential between an anode and a cathode positioned on the skin surface. This causes the migration of Na^+ and Cl^- ions from beneath the skin towards the cathode and anode, respectively [10], which generates the electric current [11]. The uncharged glucose molecules present in the interstitial fluid are carried along with the ions across the skin and collected at the cathode. Thereafter, the glucose concentration is measured using conventional glucose sensor. It has been used tremendously in various NGM devices such as GlucoWatch from Cygnus Inc., USA and Glu-Call from KMH Co., Ltd., South Korea. However, the sweating of subject can strongly interfere with the glucose measurement by this technique. Moreover, it requires a certain minimum duration so that there is enough glucose available for the measurement. But the skin irritation observed in human subjects is the major drawback of this technique.

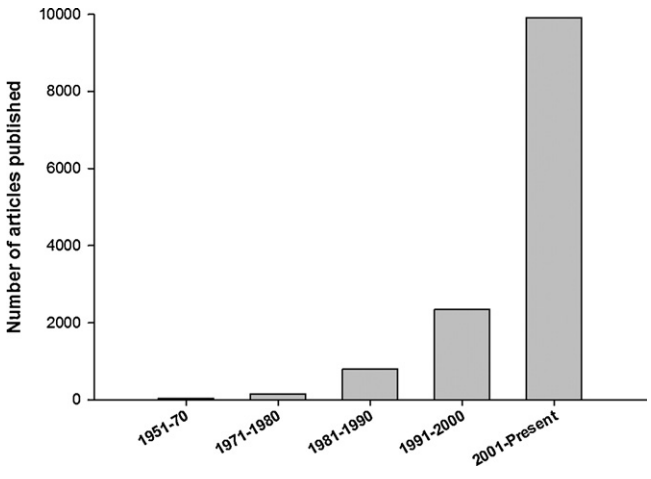

Fig. 1. Number of articles pertaining to non-invasive glucose monitoring published during the mentioned period.

Data was taken on January 14, 2012 from www.sciencedirect.com using "non-invasive" and "glucose monitoring" in the advanced search option.

Table 1
Non-invasive glucose monitoring devices.

Technology employed	Company	Device	Target site	Device characteristics
(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; and, event marking, data download, software analysis and data storage capacity *Disadvantages:* Expensive; requires 2–3 h 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; and, it shutdowns automatically in case of sweating, works better at high glucose levels and does not reliably detect hypoglycemia
Bioimpedance spectroscopy	Biovotion AG (Solianis Monitoring AG; Pendragon)	Pendra©	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 conc. and hypoglycaemia; self-correction for changes in impedance due to variations in temperature *Disadvantages:* Glucose readings vary in different 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 h equilibrium time; poor correlation of only 35% with glucose meters; Clarke EGA 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; and, 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 NGM techniques; easy calibration procedure; calibration is valid for 1 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 analyzers; and, compact and light-weight 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 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; and, good accuracy in clinical trials that was comparable to glucose meters *Disadvantages:* N.M.[a]
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; and, wireless telemetry *Disadvantages:* Requires calibration with a blood glucose meter; and, glucose measurements in interstitial fluid have time lag of 2–4 min w.r.t. 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 conc.; no skin irritation; highly successful clinical trials; good correlation with glucose analyzers and glucose meters *Disadvantages:* N.M.[a]
(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 s inside the blood vessels with high specificity and sensitivity
Impedance 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; and, no disposable waste
NIR spectroscopy	LifeTrac Systems Inc.	SugarTrac™	Skin	Blood glucose measurement in less than a min; and, safe to patient as device components do not contact the skin
NIR spectroscopy	Futrex Medical Instrumentation, Inc.	Dream Beam	Fingertip skin	Portable, compact and battery-powered but require 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 1 h before measurement and calibration with blood glucose meter after measurement
Electromagnetic sensing	ArithMed GmbH and Samsung Fine Chemicals Co. Ltd.	GluControl GC300®	Fingertip skin	Portable, battery-powered and data storage capacity

Table 1 (*Continued*)

Technology employed	Company	Device	Target site	Device characteristics
Thermal spectroscopy	Hitachi Ltd.		Fingertip skin	Compact device with integrated sensors to detect physiological parameters
Novel fluid extraction technology	Sysmex Corporation and Toshiba		Skin	Compact device with novel fluid extraction technology to provide stable interstitial fluid samples
Electromagnetic sensing	Samsung Fine Chemicals Co. Ltd.	TouchTrak Pro 200 TouchTrak HC 300	Fingertip skin	Portable device with high cost
Optical coherence tomography	GlucoLight Corporation		Skin	Portable
Fluorescence technology	GluMetrics LLC		Intravascular	Employs GluGlow technology based on a glucose-sensing polymer that glows in the presence of glucose
Thermal emission spectroscopy	Infratec Inc.		Tympanic membrane	Portable handheld device that determines blood glucose level in 10 s
Raman spectroscopy	LighTouch Medical Inc.		Fingertip skin	Portable; employs proprietary tissue modulation process for blood glucose measurements
NIR spectroscopy	MedOptix Inc.		Skin	Portable; employs proprietary ReSense technology based on the reflection of NIR light from the skin surface
Raman spectroscopy	C8 Medisensors		Skin	Compact, wearable and water-resistant; glucose measurement in 3 min; accuracy comparable to currently available continuous glucose monitoring systems; and, 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; and, CE Mark regulatory approval is still pending
Raman spectroscopy	Massachusetts Institute of Technology		Finger or arm skin	Portable; measures glucose in the interstitial fluid; employs an algorithm to determine the blood glucose level from the glucose conc. in interstitial fluid; and, 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		Finger skin	Portable device prototype that detects blood glucose in the capillaries of finger with high precision in just 1 s. Clinical testing and regulatory approvals are still needed

[a] Not mentioned

2.2. Bioimpedance spectroscopy

It is based on the measurement of impedance of a tissue using alternating currents of known intensity. The impedance (dielectric) spectrum is measured at different wavelengths and in the frequency range of 100 Hz–100 MHz. The changes in the glucose concentration of plasma change the membrane potential of red blood cells (RBCs) by varying their Na^+ and K^+ ion concentrations [12]. The changes in RBCs membrane potential are then determined by the impedance spectrum [13,14]. However, this technique has limitations as it is affected by the water content, and the disease states that affect the cell membrane. It was used in Pendra, a NGM device from Pendragon.

2.3. Thermal emission spectroscopy

This technique employs a concept similar to what is used in clinical tympanic membrane thermometers i.e. measuring the naturally emitted infrared (IR) signals that are generated in the human body due to changes in glucose concentration. The only difference is that in case of glucose monitoring, the specific wavelengths for glucose, i.e. 9.8 μm and 10.9 μm, are also added. It can determine glucose concentration in the skin of the forearm, fingertip or ear [15]. Glucose has absorptive effects on the IR radiation that are directly related to its concentration. The tympanic membrane is ideal for glucose monitoring as the glucose detection signals from the blood vessels have to cross smaller path length. The technique demonstrated good reproducibility for detecting glucose concentrations [16], but the temperature and body movements interfere strongly with the glucose detection signal. Various pathophysiological factors that induce variations in temperature interfere with glucose detection [17].

2.4. Absorbance spectroscopy

When light is focussed on the biological tissues, it reflects, scatters and transmits based on the structural and chemical composition of the sample. Therefore, most of NGM approaches are targeted to determine the optical signature of glucose, which can provide its molecular differentiation. The near-infrared (NIR) and mid-infrared (MIR) spectroscopy are the most commonly used NGM techniques.

2.4.1. Near-infrared spectroscopy

NIR spectroscopy uses a beam of light with wavelength in the range of 750–2500 nm [18–22], which is focussed on the body to estimate glucose concentration in the tissues (1–100 mm deep) by measuring variations in the light intensity due to transmission and reflectance in the tissue. The changes in glucose concentration affect the absorption and scattering coefficients of a tissue. In the NIR band, the absorption coefficient of glucose is low, which is much smaller than that of water due to the large difference in their concentrations. The absorption coefficient and concentration in this region are such that the glucose signal constitutes about only 1 part in 100,000, the major contribution being due to water. The change in the water signal with temperature over 2 °C is equivalent to the entire signal change for glucose in the clinically-relevant range. Therefore, the stronger NIR spectra of water, hemoglobin, proteins and fats overlap with the weak spectral bands of glucose. This technique has been employed to determine glucose in ear lobe, finger web, finger cuticle, skin of the forearm, lip mucosa, oral mucosa, tongue, nasal septum, cheek and arm. The NIR measurements on the finger correlated with blood glucose but were clinically unacceptable due to insufficient accuracy. However, the NIR measurements of the inner lip correlated well with a time lag of few minutes.

The technique has serious limitations as it is affected by physicochemical parameters such as changes in body temperature, blood pressure, skin hydration, and concentrations of triglyceride and albumin. Moreover, it is sensitive to environmental variations in temperature, humidity, atmospheric pressure and carbon dioxide content. The measurements are also affected by the thickness and thermal properties of the skin [23–25], and the disease states such as hyperglycaemia and hyperinsulinemia [26–28]. The NIR measurements determine the overall glucose concentration in the blood and the interstitial fluid in the tissues. But it is difficult to segregate the contribution of NIR signal due to the glucose concentration in blood or interstitial fluid.

2.4.2. Mid-infrared spectroscopy

MIR spectroscopy employs light in the spectral range of 2500–10,000 nm [15,29,16,30,31]. It is based on the same physical principle as NIR, but it has reduced scattering and increased absorption due to higher wavelengths. The MIR spectral bands produced by glucose are sharper than those of NIR, but it suffers from the same problems as NIR in addition to the strong limitation of poor penetration as light penetrates only a few micrometers inside the skin [32]. Therefore, attenuated total reflection (ATR), based on a light beam guided through a crystal by total reflection, is used to increase the penetration of light [33]. The glucose measurement is done by placing the crystal in contact with the skin using squalane oil [34], where the electromagnetic field created by the reflected light measures the glucose in the interstitial fluid in dermis [35]. The NGM devices based on NIR spectroscopy are SugarTrack (using 650 nm, 880 nm, 940 nm, and 1300 nm) and Sensys (using 750–2500 nm). Orsense employed an improved glucose measurement technique based on occlusion spectroscopy [36], where the blood flow at the fingertip is stopped temporarily using projected light at 610 nm and 810 nm. The MIR spectral measurements of blood glucose are usually done on the finger skin or oral mucosa [37] and have been shown to be dependent on the water content of the skin [32].

2.5. Photoacoustic spectroscopy

It is based on the interaction of projected laser beam with tissue cells that generates heat and causes pressure variations in the sample i.e. acoustic signals, which can be monitored by a piezoelectric transducer [38]. The selective detection of blood glucose can be done using specific wavelengths of incident laser beam [39]. The technique is not affected by water due to its poor photoacoustic response. Moreover, it can employ laser light with a wide wavelength range from ultraviolet to NIR. However, it is sensitive to changes in temperature, pressure and other environmental parameters, and is also affected by interferences from physiological substances. The technology has been employed in Aprise, a NGM device from Glucon. Aprise had good correlation with blood glucose levels. But it had non-specific interferences from other physiological substances and low sensitivity.

2.6. Raman spectroscopy

Raman spectroscopy measures the scattered light, having higher wavelength and lower intensity than the original light, in the transparent samples using visible to MIR range laser radiation source [40]. Water does not interfere with Raman spectra due to its weak scattering indexes. The separation of signals is simple as the Raman spectra are narrow and have distinct peaks [41]. However, it requires long spectral acquisition times. The instability of the laser intensity and wavelength is another limitation. An optical fibre was used to focus 785 nm beam on the anterior chamber of porcine eyes and to receive the resulting spectrum. The Raman signals in MIR range were detected from glucose in the aqueous humor. The surface-enhanced Raman spectroscopy may further increase the sensitivity of glucose detection apart from decreasing the spectral acquisition time. However, the photothermal damage to eyes needs to be critically investigated before it can be employed in humans [42].

2.7. Ocular spectroscopy

This technique measures glucose concentration in tears employing a hydrogel-bound contact lens. A 7 μm thick boronic acid derivatives based hydrogel wafer was bound to the contact lens, where the boronic acid derivatives form reversible covalent bonds with glucose in tears [43]. The lens is illuminated by a light source and the change in wavelength of reflected light, which is related to the glucose concentration in tears, is detected by a spectrometer. However, the technique suffers from potential limitations due to the uncomfortable use of contact lens, and the time lag between the glucose concentration in blood and tears. Moreover, the biocompatibility, lifetime and signal resolution still require considerable improvements. A clinical study [44] demonstrated relatively poor correlation between blood and tear glucose. Moreover, the results can be different in each eye. Therefore, it raises significant concern about how such a system would be calibrated considering that asking patients with poor eyesight and motor skills could not possibly remove 1 μL of tear from the eye using a capillary. The time lag is also a problem, especially at concentrations below 100 mg dL^{-1} (~5 mM).

2.8. Fluorescence

The technique employs the excitation of tissues by ultraviolet light at specific frequencies followed by the detection of fluorescence at a particular wavelength. The fluorescence based sensing of glucose in tears has been done using polymerized crystalline colloidal arrays that respond to different glucose concentrations through the diffraction of visible light [29]. The on-going research efforts are focussed towards the use of colored contact lenses that can change color in response to the glucose concentration. This will obviate the use of excitation and detection devices as the signal can be detected visually by comparing the color change with a precalibrated color strip [45]. In another study, an ultraviolet laser light was used to excite the glucose solution and the resulting fluorescence that was proportional to the glucose concentration was detected at 380 nm [46]. The technique has a potential advantage that the signal is unaffected by fluctuations in the light intensity of environment. However, it suffers from the same limitations as ocular spectroscopy [47,48]. Apart from the glucose concentration, the fluorescence also depends on epidermal thickness, skin pigmentation and other parameters [49]. Moreover, the use of ultraviolet laser light in tissues will also have strong scattering.

2.9. Polarimetry

The extensively use of this technique in industries for a long time to quantify the level of compounds such as glucose is the major stimulant for employing it for NGM. It is based on the rotation of linear polarization vector of light by the thickness, temperature and concentrations of the sample, when polarized light is passed through a solution containing optically active solutes such as glucose. However, the high scattering coefficients of skin cause the complete depolarization of the beam. Therefore, the aqueous humor of the eye having a clear optical media with an appropriate path length is ideal for NGM [50]. The anterior chamber of a human eye with an average width of 1 cm gives 4.562 millidegrees rotation for 5.55 mmol L^{-1} glucose at a wavelength of 633 nm [51]. The polarimetric tests in the eye has two optical paths, (i) where

it passes laterally through the cornea [52], and (ii) where the incident beam on the cornea travelling into the eyeball gets reflected by the retina and returns with information pertaining to the glucose concentration in the aqueous humor [53].

Polarimetry is unaffected by temperature and pH fluctuations. But it suffers from limitations such as interference from motion artifacts and optical noises of other substances, safety concerns for the exposure of eye to light, and requirement of technology to measure small angles. The technique has poor specificity for glucose in physiological fluids due to interference by several optically active solutes. The scattering of light by the tissues also affects the measurements. As the stratum corneum of skin lead to high scattering, it cannot be used for this technique. There is also a time lag in the glucose concentration of aqueous humor in comparison to that of blood glucose. A Faraday rotator with a single-mode flint glass fibre was employed to improve the sensitivity of the technique for glucose detection by providing a resolution of 0.55 mmol L^{-1} [54]. The procedure for the in vivo glucose measurements inside human eye was also proposed using a modified intraocular lens and a liquid-crystal polarization modulator driven by a sinusoidal signal [55,56].

2.10. Ultrasound

The technique, also known as Sonophoresis, employs a piezoelectric transducer to create 20 kHz ultrasound that increases the permittivity of skin to interstitial fluid and transports glucose to the epidermis, where it is measured by a conventional electrochemical sensor. The in vivo experiments performed in rat determined the glucose concentration in the interstitial fluid [57]. This technique is sometimes considered as minimally-invasive as it creates micropores in the skin to enable the interstitial fluid containing glucose to come outside.

2.11. Electromagnetic sensing

The changes in glucose concentration of blood change its dielectric parameters that can be detected using electromagnetic sensors based on Eddy currents [58]. The conductivity based detection of static and moving blood glucose samples inside a plastic tube at a resonant frequency of 2.664 MHz had sensitivity of 4.4 mmol L^{-1} glucose [59]. It was demonstrated that localized nuclear magnetic resonance can detect glycogen metabolism in the human brain [60]. The glucose measurements by this technique are strongly affected by changes in temperature and changes in the dielectric parameters of blood due to other physiological components.

2.12. Temperature-regulated localized reflectance

It analyses the temperature modulation of localized reflected light due to scattering. The glucose concentration in the dermis is estimated by measurements on the skin of forearm. The variations in temperature cause changes in the refractive index of tissues that affect the light scattering depending upon glucose concentration, which is estimated with localized reflectance signals at 590 nm and 935 nm [29]. In some reports, a probe was placed in contact with the skin and its temperature was varied between 22 °C and 38.8 °C. The skin was equilibrated for some minutes after each variation and some light packets related to the glucose concentration were collected [17]. However, several physiological parameters, probe position, and several disease conditions such as those associated with fever can affect the glucose measurement.

2.13. Optical coherence tomography

The optical coherence tomography (OCT) is similar to the light scatter technique (localized reflectance) as it exploits the scattering of light. However, it is based on the delay of backscattered light compared to the light reflected by the reference arm mirror, while the light scatter technique employs the intensity of collected light. The glucose concentrations determined by OCT on the basis of the scattering coefficients were similar to those measured by light scatter technique. However, it has limitations as it is sensitive to motion artefacts and changes in skin temperature. It has been employed to measure glucose concentration in the interstitial fluid of upper dermis of skin in forearm.

It employs a low coherence light, an interferometer having a reference and a sample arm, a moving mirror in the reference arm, and a photodetector to measure the interferometric signal [61]. The photodetector detects the interferometric signal obtained by the combination of backscattered light from tissues in the sample arm and reflected light in the reference arm of interferometer [29]. It can obtain high resolution two-dimensional images by in-depth and lateral scanning. The scanning of in-depth tissues (up to 1 mm depth) and tissue surface are done by moving the mirror into the reference and sample arm of the interferometer, respectively. The refractive index of the interstitial fluid increases in response to increase in its glucose concentration and changes its scattering coefficient, which is used to determine its glucose concentration.

2.14. Metabolic heat conformation

It involves measurements of thermal generation, blood flow rate, hemoglobin, and oxyhemoglobin concentrations, which correspond to the blood glucose levels [62]. However, it is used as an auxiliary technique for glucose quantification as it has strong probability of interfering with the environmental conditions. The initial tests measured the temperature at the fingertip, ambient room, and background radiation. The multiwavelength spectroscopy at various wavelengths (470 nm, 535 nm, 660 nm, 810 nm, 880 nm, and 950 nm) was also used to improve glucose measurements. Hitachi is working on improving the performance of a developed glucose sensor prototype that is based on this technique [63].

3. Non-invasive glucose monitoring devices

3.1. GlucoWatch® G2 biographer

GlucoWatch® G2 biographer from Cygnus Inc., California, USA was the main NGM device in the form of a wrist-watch. Cygnus received CE certification in 1999 followed by FDA approval in 2001. But the device was approved as a supplementary to conventional blood glucose meters to detect glucose level trends and track patterns in diabetics. The glucose measurement was done by reverse iontophoresis [64] based extraction of interstitial fluid through the skin. This was done by directing 300 μA electric current between two electrodes contacting the skin on the backside of the device. It enables the taking out of interstitial fluid into two collection disks that act as anode and cathode. The glucose molecules are extracted through the epidermis to the iontophoretic cathode along with Na^+ ions by electro-osmosis. The amperometric biosensor has to detect 50–200 pmol glucose as the use of mA currents extracts glucose in μM ranges. The biosensor detects H_2O_2 generated by GOx-catalyzed reaction using nA currents [65]. The detection of glucose also takes into account the skin temperature and perspiration fluctuations by employing thermo transducers and conductivity sensors in the device [66]. The glucose detection was done with a 15 min time lag compared to the standard blood glucose measurements by an enzyme reaction as found in a glucose meter. It requires 2–3 h warm-up period [67,68] and can do six glucose measurements per hour. It is equipped with alarm for greater than 35% change in glucose readings; a trend indicator for change of

1 mmol L^{-1}; event markers for activities such as meals, exercise and insulin intake; data download to PC and software analysis; and, internal memory to store up to 8500 readings. However, it has limitations such as the requirement of calibration using a standard blood glucose meter; replacement of disposable pad every 12 h; need for warm-up period followed by calibration; inaccurate glucose measurements if the patient is moving, exercising, sweating or having rapid temperature changes; and, inability to use the device in water i.e. swimming, shower or bath during the warm-up period. The meter has been found to cause skin irritation and thus a different site is used every week. The skin reactions was cited as the main reason for the failure of device as participants in the study developed low to moderately severe skin reactions. The glucose measurements by the device were more painful due to the skin irritation, which was problematic for younger children where it was used for nocturnal monitoring. The other serious problem was the automatically shut down of the device in case of sweating. Since sweating is a symptom of hypoglycemia, the device shuts down precisely when monitoring is most needed. Moreover, it was three times more expensive than the standard glucose meter. The clinical studies showed that the device performs better at high glucose levels but do not reliably detect hypoglycemia [69]. The monitoring of decreasing glucose is often more important as the main driving force for type 1 patients is to avoid hypoglycemia. Cygnus Inc. went out of business in 2004 and was sold to Animas Corporation and Animas Technologies LLC for US$ 10 million in March, 2005. However, due to continuous problems with the device, the sale of GlucoWatch® G2 Biographer was ceased on July 31, 2007. It is to be noted that Glucowatch is not considered as a truly "non-invasive" device by many persons. However, it is significant in the development of NGM technology.

3.2. *Pendra*®

Pendra® from Pendragon Medical Ltd., Switzerland was another NGM device in the form of a wrist-watch, which was based on impedance spectroscopy. It was approved by CE in May, 2003 as an adjunctive device to standard blood glucose meters to detect trends and patterns in glucose levels. It was based on the technology developed by Caduff's group in 2003. It consists of an open resonant circuit (1–200 MHz) that lies in contact with skin with the help of a tape on the backside of the device and performs the impedance measurements. It can perform up to four measurements per minute with sensitivity in the range of 20–60 mg dL^{-1} glucose per ohm. It has USB connectivity for downloading data to a PC; Pendra User software for data analysis; Patient and Physician softwares for diabetic management; data storage capacity for up to 1 month; battery lasting up to 24 h; self-correction for changes in impedance due to variations in temperature; and, ability to provide alerts for rapid changes in glucose concentration and hypoglycemic events. However, the device did not perform well in market due to variations in the readings in different individuals, and the requirement of additional calibration for differences in skin and underlying tissues among individuals. The patient-tailored calibration procedure is required prior to use and would last 2–3 days. About 30% of the patients have to discontinue the use of device after calibration as their skin types and basic skin impedances are unsuitable for the device. The Pendra tape needs to be changed every 24 h. The device needs to be reattached at the same spot where it was calibrated, which is followed by 1 h equilibration time. The correlation studies showed a poor correlation of only 35.1% w.r.t. commercial glucose meters. The Clarke error grid analysis (EGA) indicated that 78.4%, 6.5%, 10.8%, and 4.3% of the Pendra's readings were in the A + B, C, D and E zone, respectively [70]. The mean absolute difference compared with capillary blood glucose values was 52%. Moreover, it has a potential limitation that the patient must rest for 60 min for equilibration before the glucose measurements can be made [71]. It was only suitable for specific persons whose local dielectric skin had a minimum resonance frequency [72]. The production of Pendra was stopped as the company went bankrupt in 2005. However, the bioimpedance work of Caduff's group was still investigated by Solianis Monitoring AG, Zurich, Switzerland [73]. Biovotion AG, Zurich, Switzerland acquired Solianis intellectual property portfolio in Oct., 2011. Biovotion is developing a multisensory concept for the continuous non-invasive monitoring of health parameters.

3.3. *GlucoTrack*™

GlucoTrack™ was a handheld real-time continuous NGM device (Fig. 2) developed by Integrity Applications Ltd., Israel. It determines glucose concentration in the blood by employing three NGM techniques i.e. ultrasonic, electromagnetic and heat capacity [74]. It has high precision and accuracy as the combination of various technologies minimizes the noise in measurements by minimizing the effect of interferences. The device measures glucose concentration in the earlobe by attaching personal ear clip (PEC) equipped with sensors and calibration electronics (Fig. 2(B)). The earlobe is an easily accessible site with abundant blood supply and is not affected by routine activities. It requires an individual calibration against invasive basal and post-prandial blood glucose references before it can be used for glucose measurements. But the calibration remains valid for about one month. It demonstrated a high accuracy in clinical trials [75] as the readings correlated well with those of commercial glucose meter and glucose analyzer. Based on the Clarke EGA, 92% of the readings were in the clinically acceptable A and B zones. It has USB and IR connectivity, battery recharge, alerts for hypo- and hyperglycaemia, multi-user support, internal memory for storing up to 1000 readings per user, large LCD screen, and software for data processing and analysis. The device is compact, lightweight, and totally safe to patients. But it has not been commercialized as the company wanted to enhance its performance by improving the quality of calibration procedure and algorithm employed for data processing. However, as per their website information, the company intends to bring the device to the market in 2012.

3.4. *OrSense NBM-200G*

OrSense NBM-200G is a CE approved device from OrSense Ltd., Israel that allows non-invasive measurement of glucose as well as hemoglobin and oxygen saturation with very high sensitivity. It employs red NIR occlusion spectroscopy, which is based on detecting the red NIR optical signal of blood due to changes in the glucose concentration in blood vessels of finger. The temporary cessation of blood flow to the finger in occlusion enhances the red NIR signal, thereby improving the signal-to-noise ratio. The device is portable, easy-to-use, and measures glucose in less than a minute. It has internal memory to store up to 500 readings, alarm alerts, trend data analysis, integrated wireless telemetry, and easy-to-read display. It measures glucose continuously for up to 24 h and does not require frequent calibrations. It is completely safe for patients without any risk of contamination. According to the information available on the company's website, the device was tested in over 400 subjects, where it was found to have accuracy comparable to that of invasive glucose meters. It enabled the identification of glucose trends and the detection of hypo- and hyperglycemia events. A clinical trial was also conducted at the Sheba Medical Center, Israel and in an outpatient clinic. The Clarke EGA showed 95.3% of all points in the A + B zones, 4.7% points in C + D zones, and no points in the E zone. The investors in OrSense non-invasive monitoring technologies were Israel Health Care Ventures and STAR Ventures.

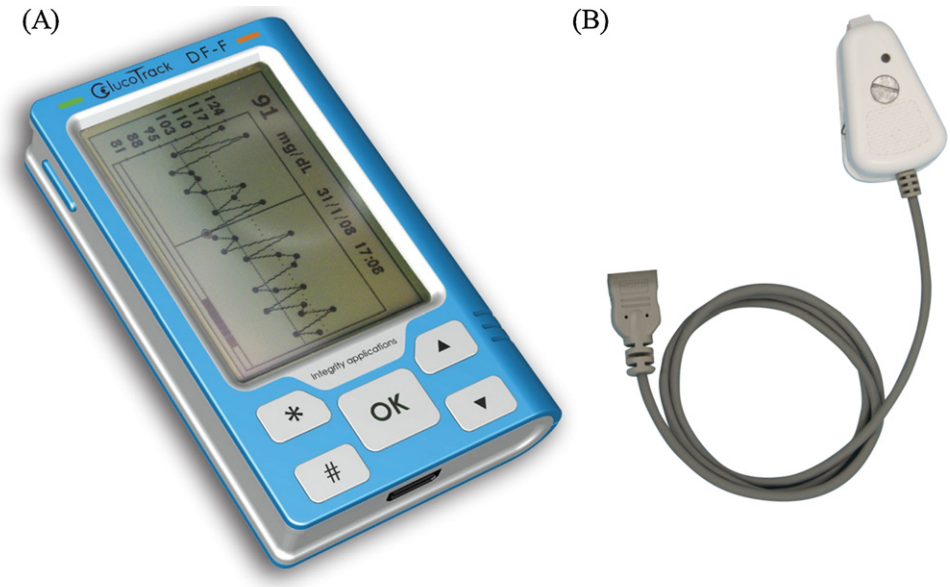

Fig. 2. GlucoTrack™ non-invasive glucose monitoring device [74]. (A) Main unit. (B) Personal ear clip. Image provided by Avner Gal, Integrity Applications.

The device received the Frost & Sullivan's 2006 Technology Innovation award. However, the system has not been commercialized and is being utilized for investigation and market awareness purposes only.

3.5. SpectRx Inc.

SpectRx Inc. at Norcross, Georgia, USA developed a biophotonics-based NGM device, which employs a handheld Altea MicroPor™ laser to create micropores in the stratum corneum i.e. the outermost layer of skin through which the interstitial fluid comes out and gets collected in an external patch on the skin containing glucose sensor. The inexpensive low-energy laser has a self-regulating feature that prevents any damage to the viable tissues beneath the outermost dead layer of the skin. It has a wireless transmitter and a handheld display. The glucose measurements in the interstitial fluid by this device correlated well with the blood glucose measurements done with a commercial analyzer and glucose meters. It can detect glucose in the interstitial fluid in the range of 60–400 mg dL^{-1}. The device is calibrated with a blood glucose meter. The glucose measurements in the interstitial fluid have a time lag of 2–4 min in comparison to that in the blood. The SpectRx NGM technology was licensed to Abbott Laboratories, which funded the research and development at SpectRx. The name of the company was changed to Guided Therapeutics, Inc. in May, 2008 and the major focus of the company was shifted towards the non-invasive detection of cervical precancer and cancer. It developed LuViva® advanced cervical scan, which differentiates between the diseased and normal tissue by analyzing the light reflected from the cervix.

3.6. Symphony®

Symphony® is a continuous NGM device developed by Sontra Medical Corporation, which employs a standard glucose sensor to monitor transdermal glucose levels in patients with high accuracy using a simple wireless system. On September 17, 2007, Sontra Medical Corporation was merged with Echo Therapeutics, Inc., a specialty transdermal therapeutics company, to operate under the name of Echo Therapeutics, Inc. The technology involves permeation of the skin by a special transdermal permeation system called Prelude® SkinPrep and a brief warm-up period followed by the glucose measurement every minute on the permeated site using a biosensor. The data is transmitted wirelessly to a remote monitor that is equipped with alarm alerts if the glucose level goes outside the normal range. The device does not cause any skin irritation. The company announced highly successful clinical trials for the device in October, 2011, which demonstrated improved clinical performance. The glucose measurement performed by this device correlated well with the blood glucose measurements done using YSI 2300 STAT Plus glucose analyzer and commercial glucose meter. There are no reported discomfort or safety concerns for the device. The results presented to the press by the company in January 2012 were very encouraging. The mean absolute relative difference (MARD) of 12.6% and 96.9% values in the A + B zones of the EGA were obtained on 20 volunteers. However, these results were not peer-reviewed. Another very interesting study was also performed where patients having just experienced cardiac surgery were monitored for their glucose levels using this system. It was observed that the health of trauma patients is improved if their glucose levels are maintained within a narrow range.

3.7. Other devices

Diasensor® was developed by Biocontrol Technology, Inc. as a supplementary to the standard blood glucose meters. It enables glucose measurement in less than 2 min by placing the patient's forearm on the arm tray of the device. However, it had relatively large size and could not detect hypoglycaemic events. The device did not work properly and its production was stopped in 2002 due to various technology concerns and financial limitations.

Several NGM devices have been developed but not commercialized due to unknown reasons. These include Aprise™ by Glucon Medical Ltd., Israel; Glucoband® by Calisto Medical Inc., USA; SugarTrac™ by LifeTrac Systems Inc., USA; Dream Beam by Futrex Medical Instrumentation, Inc., USA; GluCall from KMH Co. Ltd., Korea; GluControl GC300® by ArithMed GmbH, Germany that was developed together with Samsung Fine Chemicals Co. Ltd., Korea; Hitachi Ltd., Japan; Sysmex Corporation, Japan; TouchTrak Pro 200 and TouchTrak HC 300 by Samsung Fine Chemicals Co. Ltd, Korea; and, NGM devices by Infratec Inc., USA; GluMetrics LLC, USA;

Fig. 3. HG1-c continuous non-invasive glucose monitoring device developed by C8 Medisensors [73].
Image provided by Paul Connolly, C8 Medisensors.

GlucoLight Corporation, USA; LighTouch Medical Inc., USA; and, MedOptix Inc., USA.

Some of these NGM devices were tested clinically. Aprise™ was tested in 62 diabetic patients and was shown to provide promising results [76]. The Clarke EGA indicated 66.5%, 28.1%, 1%, 4.4%, and 0% readings in the A, B, C, D and E zones, respectively. Based on the website information, a clinical trial was also conducted for Glucoband® at the City of Angels Hospital in Los Angeles, California on 44 subjects. The Clark EGA indicated 79% and 21% readings in the zones A and B, respectively with. There were no readings in the zones C, D and E. The correlation coefficient of the glucose measurements by Glucoband® with those made by AccuCheck glucose meter was also 0.89. However, there studies were not peer-reviewed. The commercial prototype was planned for 2011 but was never released. The clinical trials for SugarTrac™, conducted at Brigham Women's Hospital in Cambridge, Massachusetts were unsuccessful and stressed the need to overcome difficulties in the mechanical design. GluCall was clinically tested at Ajou University hospital, South Korea, where its glucose readings correlated well with the actual blood glucose readings taken from the venous blood. However, again there were not peer-reviewed studies.

3.8. Ongoing developments

C8 MediSensors is San Jose, California, USA based company that developed compact continuous NGM device i.e. HG1-c (Fig. 3), which is based on Raman spectroscopy. The device is for investigational use at the moment. It is water-resistant but not water-proof, performs a single glucose measurement in about 3 min, and has been claimed to be comparable in accuracy to the currently available continuous glucose monitoring systems. The cost of glucose determination is also claimed to be less than 3 finger-stick tests per day over 4 years. In a recent press release [77], C8 MediSensors raised a total of US$ 24 million through the sale of preferred C stock. The existing and the new investors that include GE Healthcare made a significant investment that will accelerate C8 MediSensors' planned product introduction in 2012. The investment by GE Healthcare through its healthymagination Fund will be a strategic advantage to C8 MediSensors in terms of taking the technology to the diabetic patient. The company will introduce its NGM device in Europe in 2012, pending CE Mark regulatory approval.

A group of researchers at Massachusetts Institute of Technology are developing a Raman spectroscopy based NGM device [78],

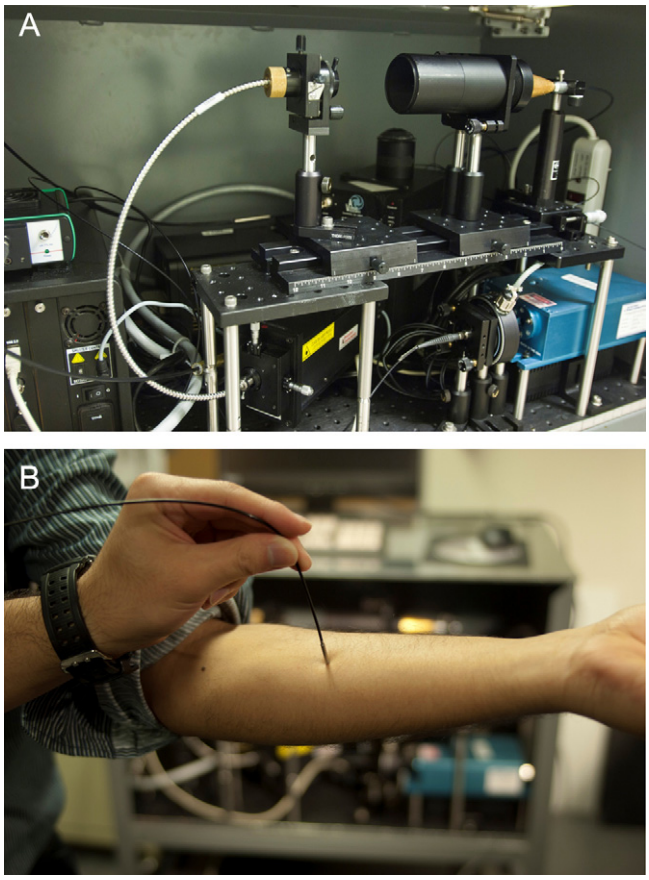

Fig. 4. (A) Raman spectroscopy based non-invasive glucose monitoring device prototype developed by a group of researchers at Massachusetts Institute of Technology, and (B) its use for non-invasive glucose monitoring in the interstitial fluid.
Image provided by Ishan Barman, Massachusetts Institute of Technology.

which measures glucose levels in interstitial fluid by scanning the finger or arm with NIR light that can penetrate only 0.5 mm below the skin (Fig. 4). The device is a miniaturized laptop-sized Raman spectroscopy machine. The group developed an algorithm to determine the blood glucose level from the glucose concentration in interstitial fluid. They developed a Dynamic Concentration Correction (DCC) based calibration procedure (Fig. 5) that improves the precision of blood glucose measurements by taking into account the rate of glucose diffusion from the blood into the interstitial fluid [79].

A group of researchers at University of Missouri-St. Louis (UMSL), USA have developed a portable NGM detector [80] that detects blood glucose in the capillaries of finger with high precision in just one second, which is the fastest glucose detection time reported for NGM. A NIR light is shined through the finger and the light transmitted through the finger is detected. The output signal is then provided to a processor that determines the glucose concentration. The technology has been licensed to St. Louis Medical Devices situated at UMSL startup company incubator. The company will do the clinical testing and get the approvals for the device before bringing it to the market.

4. Key challenges

The key challenges in the development of NGM devices are the improvement of signal-to-noise ratio (SNR) and sensitivity, development of wearable continuous NGM systems, evaluation of analytical performance, development of procedures for highly

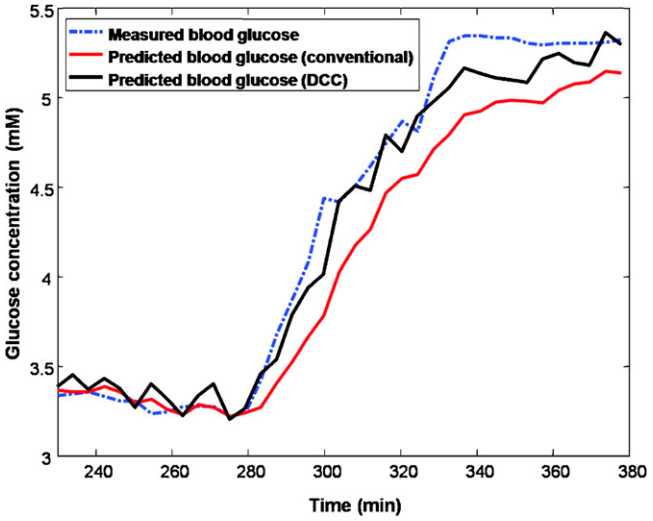

Fig. 5. Prospective prediction results of conventional and Dynamic Concentration Correction (DCC)-based calibration methods applied to the simulated data set [75]. The measured blood glucose concentration values are given by the blue dotted line. Reprinted with permission from ACS Publications. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

precise blood glucose determination, and reducing the time taken for glucose measurement.

The signal-to-noise ratio (SNR) and the sensitivity of NGM devices can be improved by employing next-generation of transducers and methods that can do the parallel monitoring of multiple parameters. The simultaneous monitoring of bioimpedance and NIR spectroscopy has been demonstrated in the skin. GlucoTrack™ from Integrity Applications determines the blood glucose concentration using various techniques i.e. ultrasound, conductivity, and heat capacity. The increase in sensitivity of each of the techniques and reducing the contribution of noise improves the SNR. The SNR in data can be further improved using digital filters and data treatment methods such as ridge regression, artificial neural networks, principal component analysis and partial least squares.

The development of wearable continuous NGM system is also a major challenge. However, it will be of tremendous value as it can eliminate the issues of biocompatibility and pain along with other concerns that are presently associated with the current continuous glucose monitoring systems. The recent development of wearable continuous NGM device HG1-c by C8 MediSensors is a major achievement in this direction.

The analytical performance of the developed NGM device needs to be evaluated in terms of the accepted guidelines i.e. the Error-Grid Analysis [81,82] and International Organization for Standardization (ISO) Standards [83]. There need to be a good correlation of the glucose measurements performed by the developed NGM device with those performed by the established technologies i.e. glucose analyzers and glucose meters. The other commonly employed parameter for characterizing sensor performance is the Mean Absolute Relative Difference (MARD) [84], which should be below 15% to be considered acceptable. The current requirements for the blood glucose monitoring by glucose meters is that 95% of the glucose measurements by the device should fall within $\pm 15\ mg\ dL^{-1}$ of a reference measurement of glucose concentration $<75\ mg\ dL^{-1}$, and within ±20% at glucose concentrations $>75\ mg\ dL^{-1}$.

There is a need to develop procedures for determining the blood glucose levels from the glucose concentration in other physiological fluids such as interstitial fluid. Several groups have developed DCC-based calibration procedures [79] for the highly precise blood glucose determination. However, a full clinical study is still required to validate these findings. The dynamic correlation methods may not necessarily be as useful because the "lag" between blood and tissue glucose also depends on the site of measurement, on individual patient characteristics, which may change, and on whether the glucose is increasing or decreasing. It is to be noted that there is time lag induced by the glucose measurement process itself apart from the physiological time lag for the glucose to pass from the blood to the glucose measurement site. The blood glucose might not actually be the most relevant physiologically important parameter as capillary blood might be better. But it is used as the standard due to its ease of measurement. Though far from perfect, the invasive devices have performed better than the "optical" devices because they come closer to sampling blood glucose.

Presently, the time taken for glucose measurement by many NGM techniques is undoubtedly much higher than the time taken by glucose meters. This is a limitation with several NGM techniques. However, the recent development of a portable NGM device that measures glucose in just 1 s [80] is a key achievement.

The inherent lack of specificity in certain NGM technologies, weak signal, and interference from absorption and scattering of other tissue components are some of the other issues that need to be addressed. The ongoing research efforts by many groups will certainly provide the essential tools to tackle these challenges in NGM. However, despite all these challenges and concerns of the technology, there have been significant developments in the field of NGM.

5. Conclusions and future trends

Diabetes is increasing worldwide at an alarming pace of 7.8 million persons developing diabetes each year. It incurred 11.6% of the total global healthcare expenditure amounting to 418 million international dollars in 2010 [1]. The frequent monitoring of glucose is the most important part of diabetic management as it is the only way by which the diabetics can keep their blood glucose level within the physiological range. This will enable them to live a healthy life by avoiding diabetes-associated life-threatening complications. Several research efforts have been devoted to find the cure for diabetes by the development of artificial pancreas or by islet cell transplantation. But it will take a lot of time based on the challenges involved and only a very limited scope for success. The painless NGM will enable the diabetics to monitor their blood glucose more frequently. However, despite continuous developments in the technology for NGM, more intensive research efforts are still required to develop robust NGM devices for highly precise glucose measurements.

The widely-employed electrochemical glucose meters are "finger stick systems" that require less than 1 μL of blood obtained with a 32 gauge lancet. Therefore, obtaining the blood sample is not so painful and does not necessarily require the finger as the sampling site. The associated strips can be made so reproducibly that calibration is no longer necessary. The measurements are very rapid (a few seconds) and the measurement system can easily be contained within a pocket. Thus, the glucose values can be obtained discretely during the day and stored on the associated meter. The strips are yet a bit expensive (often 1 USD each), but the prices are coming down. But the real value will be in the development of wearable continuous glucose monitoring systems, as avoiding the biocompatibility issues for indwelling sensors is a major problem that has only partly been solved. However, few if any of the viable non-invasive systems seem to be even designed for this purpose.

The non-invasive devices have tremendous appeal and a market in excess of at least US$ 1 billion per year worldwide. However, the development of non-invasive devices has been hampered by

unsubstantiated claims, which proved to be misleading if not false [70]. This has undermined confidence in such technology within the diabetes community. Presently, the NGM devices are not being used by diabetics due to the lack of precision, robustness, stability and analytical performance in comparison to conventional blood glucose meters. The NGM technology still requires tremendous improvements in order to address the challenges, which include rapid response; elimination of interferences; higher precision; and, improved calibration, cost-effectiveness, comfort and patient safety. Apart from this, the softwares and the device features need to be continuously evolved. However, the developments in NGM technology requires a substantial amount of continuous R&D funding that can only be afforded by the industrial giants such as Abbott, LifeScan, Bayer, Roche, Minimed/Medtronic or Dexcom.

However, on the other hand, the developments in non-invasive monitoring have successfully paved way for several potential applications in diabetic screening. VeraLight Inc. is a privately held medical instrumentation company in New Mexico. It received the CE Mark approval for its SCOUT DS® device for non-invasive diabetic screening in Aug., 2011, and Health Canada Licence approval in Apr., 2011. The company intends to apply for FDA approval in 2012. The company has received US$ 5 million Series D funding by Psilos Group and CMEA Capital along with other investors i.e. vSpring Capital and InLight Solutions. This is to support the SCOUT DS® market rollout in Canada, Middle East, India and selected European countries. The device enables the widespread screening of population prior to the onset of prediabetes (impaired glucose tolerance) and Type 2 diabetes, when it is still possible to avoid the disease. The measurement is done in 3 min by placing patient's forearm onto the portable table-top unit. It is economical, non-invasive, non-fasting, and is more sensitive than the blood testing. The device detects the biomarkers in skin, which are related to glucose concentration, oxidative stress and microvascular changes, using a proprietary technology to measure skin fluorescence. SCOUT Diabetic Score is determined from the skin fluorescence by using a proprietary algorithm that also adjusts for changes in skin tone. However, the device is not as easily portable as the commercial glucose meter. However, these non-invasive monitoring devices are still not so appealing. Tremendous research efforts are needed to develop a reliable continuous monitoring device that is portable, wearable and unobtrusive. The only devices that have met these criteria, albeit only partially, are the FDA-approved electrochemical systems.

The blood glucose meters have already reached the advanced stage in terms of analytical performance, cost-effectiveness, convenience, software based data analysis and management, and sophisticated device features. Therefore, further improvement in blood glucose meters seems unnecessary. In fact, many companies have now started working on the interface of glucose meters with mobiles. One such development has been made possible by Progical Solutions LLC, which have developed the technology to interface the glucose meters to iPhone using the 3.5 mm audio jack [85]. On the other hand, the field of NGM is still developing and needs tremendous improvements before it can lead to the development of next-generation of pain-free NGM devices for diabetics. However, the developments made till date in NGM have proved to be very useful for diabetic screening.

References

[1] P. Zhang, X. Zhang, J. Brown, D. Vistisen, R. Sicree, J. Shaw, G. Nichols, Diab. Res. Clin. Pract. 87 (2010) 293–301.
[2] S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Diab. Care 27 (2004) 1047–1053.
[3] D.R. Whiting, L. Guariguata, C. Weil, J. Shaw, Diab. Res. Clin. Pract. 94 (2011) 311–321.
[4] L. Guariguata, D.R. Whiting, C. Weil, N. Unwin, Diab. Res. Clin. Pract. 94 (2011) 322–332.
[5] http://www.researchandmarkets.com/reports/338842/biosensors_in_medical_diagnostics_global, 2012.
[6] S.K. Vashist, D. Zheng, K. Al-Rubeaan, J.H.T. Luong, F.-S. Sheu, Anal. Chim. Acta 703 (2011) 124–136.
[7] A. Tura, A. Maran, G. Pacini, Diab. Res. Clin. Pract. 77 (2007) 16–40.
[8] C.E.F.D. Amaral, B. Wolf, Med. Eng. Phys. 30 (2008) 541–549.
[9] B. Leboulanger, R.H. Guy, M.B. Delgado-Charro, Physiol. Meas. 25 (2004) R35–R50.
[10] R.T. Kurnik, J.J. Oliver, S.R. Waterhouse, T. Dunn, Y. Jayalakshmi, M. Lesho, M. Lopatin, J. Tamada, C. Wei, R.O. Potts, Sens. Actuators B: Chem. 60 (1999) 19–26.
[11] K.R. Pitzer, S. Desai, T. Dunn, S. Edelman, Y. Jayalakshmi, J. Kennedy, J.A. Tamada, R.O. Potts, Diab. Care 24 (2001) 881–885.
[12] T.A. Hillier, R.D. Abbott, E.J. Barrett, Am. J. Med. 106 (1999) 399–403.
[13] I. Ermolina, Y. Polevaya, Y. Feldman, Eur. Biophys. J. 29 (2000) 141–145.
[14] Y. Polevaya, I. Ermolina, M. Schlesinger, B.Z. Ginzburg, Y. Feldman, Biochim. Biophys. Acta 1419 (1999) 257–271.
[15] O.S. Khalil, Clin. Chem. 50 (2004) 2236–2237.
[16] C.D. Malchoff, K. Shoukri, J.I. Landau, J.M. Buchert, Diab. Care 25 (2002) 2268–2275.
[17] S.J. Yeh, C.F. Hanna, O.S. Khalil, Clin. Chem. 49 (2003) 924–934.
[18] S.F. Malin, T.L. Ruchti, T.B. Blank, S.N. Thennadil, S.L. Monfre, Clin. Chem. 45 (1999) 1651–1658.
[19] K. Maruo, M. Tsurugi, J. Chin, T. Ota, H. Arimoto, Y. Yamada, M. Tamura, M. Ishii, Y. Ozaki, IEEE J. Sel. Top Quant. Electron. 9 (2003) 322–330.
[20] W. Schrader, P. Meuer, J. Popp, W. Kiefer, J.U. Menzebach, B. Schrader, J. Mol. Struct. 735–736 (2005) 299–306.
[21] S. Kasemsumran, Y. Du, K. Maruo, Y. Ozaki, Chemom. Intel. Lab. Syst. 82 (2006) 97–103.
[22] D.D. Cunningham, J.A. Stenken (Eds.), In Vivo Glucose Sensing, John Wiley & Sons, Inc., New Jersey, 2010 (Chapter 13: Near-infrared spectroscopy for non-invasive glucose sensing).
[23] R.G. Sibbald, S.J. Landolt, D. Toth, Endocrinol. Metab. Clin. North Am. 25 (1996) 463–472.
[24] V.M. Monnier, O. Bautista, D. Kenny, D.R. Sell, J. Fogarty, W. Dahms, P.A. Cleary, J. Lachin, S. Genuth, Diabetes 48 (1999) 870–880.
[25] S.J. Yeh, O.S. Khalil, C.F. Hanna, S. Kantor, J. Biomed. Opt. 8 (2003) 534–544.
[26] H. Yki-Jarvinen, T. Utriainen, Diabetologia 41 (1998) 369–379.
[27] P.H. Oomen, G.D. Kant, R.P. Dullaart, W.D. Reitsma, A.J. Smit, Microvasc. Res. 63 (2002) 1–9.
[28] G. Mazarevica, T. Freivalds, A. Jurka, J. Biomed. Opt. 7 (2002) 244–247.
[29] R. Fusman, R. Rotstein, K. Elishkewich, D. Zeltser, S. Cohen, M. Kofler, Acta Diabetol. 38 (2001) 129–134.
[30] W.B. Martin, S. Mirov, R. Venugopalan, J. Biomed. Opt. 7 (2002) 613–618.
[31] Y.C. Shen, A.G. Davies, E.H. Linfield, T.S. Elsey, P.F. Taday, D.D. Arnone, Phys. Med. Biol. 48 (2003) 2023–2032.
[32] L. Brancaleon, M.P. Bamberg, T. Sakamaki, N. Kollias, J. Invest. Dermatol. 116 (2001) 380–386.
[33] L.M. Harvey, B. McNeil, Anal. Chim. Acta 561 (2006) 218–224.
[34] K. Tamura, K. Fujita, W. Kaneko, N.T.N.T. Linh, H. Ishizawa, E. Toba, Instrumentation and Measurement Technology Conference, 2004, Proc. 21st IEEE, vol. 3, 2004, pp. 1970–1974.
[35] S.N. Thennadil, J.L. Rennert, B.J. Wenzel, K.H. Hazen, T.L. Ruchti, M.B. Block, Diab. Technol. Ther. 3 (2001) 357–365.
[36] O. Cohen, I. Fine, E. Monashkin, A. Karasik, Diab. Technol. Ther. 5 (2003) 11–17.
[37] H.M. Heise, R. Marbach, Cell Mol. Biol. (Noisy-le-grand) 44 (1998) 899–912.
[38] Y. Wickramasinghe, Y. Yang, S.A. Spencer, J. Fluoresc. 14 (2004) 513–520.
[39] T.J. Allen, B.T. Cox, P.C. Beard, Proc. SPIE 5697 (2005) 233–242.
[40] D.I. Ellis, R. Goodacre, Analyst 131 (2006) 875–885.
[41] A.J. Berger, I. Itzkan, M.S. Feld, Spectrochim. Acta A 53 (1997) 287–292.
[42] A. Ergin, G.A. Thomas, Chapter title, in: 31st IEEE Annual Northeast Bioengineering Conference, Hoboken, April 2–3, 2005, pp. 246–247.
[43] A. Domschke, W.F. March, S. Kabilan, C. Lowe, Diab. Technol. Ther. 8 (2006) 89–93.
[44] J.T. Baca, C.R. Taormina, E. Feingold, D.N. Finegold, J.J. Grabowski, S.A. Asher, Clin. Chem. 53 (2007) 1370–1383.
[45] R. Badugu, J.R. Lakowicz, C.D. Geddes, Cur. Opin. Biotechnol. 16 (2005) 100–107.
[46] O.S. Khalil, Diab. Technol. Ther. 6 (2004) 660–697.
[47] W. March, D. Lazzaro, S. Rastogi, Diab. Technol. Ther. 8 (2006) 312–317.
[48] E.A. Moschou, B.V. Sharma, S.K. Deo, S. Daunert, J. Fluoresc. 14 (2004) 535–547.
[49] J. Sandby-Moller, T. Poulsen, H.C. Wulf, Photochem. Photobiol. 77 (2003) 616–620.
[50] B.D. Cameron, J.S. Baba, G.L. Cote, Diab. Technol. Ther. 3 (2001) 201–207.
[51] G.C. Cote, J. Nutr. 131 (2001) 596S–604S.
[52] R.J. McNichols, G.L. Cote, J. Biomed. Opt. 5 (2000) 5–16.
[53] S. Jang, M.D. Fox, Bioengineering Conference, 1997, Proc. IEEE 1997 23rd Northeast, 1997, pp. 11–12.
[54] M. Yokota, Y. Sato, I. Yamaguchi, T. Kenmochi, T. Yoshino, Meas. Sci. Technol. (2004) 143–147.
[55] R. Rawer, W. Stork, C.F. Kreiner, Graefe's Arch. Clin. Exp. Ophthalmol. 242 (2004) 1017–1023.
[56] Y.L. Lo, T.C. Yu, Opt. Commun. 259 (2006) 40–48.
[57] S. Lee, V. Nayak, J. Dodds, M. Pishko, N.B. Smith, Ultrasound Med. Biol. 31 (2005) 971–977.
[58] S.M. Alavi, M. Gourzi, A. Rouane, M. Nadi, Proceedings of the 23rd Annual International Conference of the IEEE, Istanbul, October 25–28, 2001, vol. 4, 2001, pp. 3318–3320.

[59] M. Gourzi, A. Rouane, R. Guelaz, M.S. Alavi, M.B. McHugh, M. Nadi, P. Roth, J. Med. Eng. Technol. 29 (2005) 22–26.
[60] G. Oz, P.G. Henry, E.R. Seaquist, R. Gruetter, Neurochem. Int. 4 (2003) 323–329.
[61] K.V. Larin, M.S. Eledrisi, M. Motamedi, R.O. Esenaliev, Diab. Care 25 (2002) 2263–2267.
[62] O.K. Cho, Y.O. Kim, H. Mitsumaki, K. Kuwa, Clin. Chem. 50 (2004) 1894–1898.
[63] J.B. Ko, O.K. Cho, Y.O. Kim, K. Yasuda, Diab. Care 27 (2004) 1211–1212.
[64] R.O. Potts, J.A. Tamada, M.J. Tierney, Diab. Metab. Res. Rev. 18 (2002) S49–S53.
[65] M.J. Tierney, Y. Jayalakshmi, N.A. Parris, M.P. Reidy, C. Uhegbu, P. Vijayakumar, Clin. Chem. 45 (1999) 1681–1683.
[66] M.J. Tierney, J.A. Tamada, R.O. Potts, L. Jovanovic, S. Garg, Biosens. Bioelectron. 16 (2001) 621–629.
[67] R. Panchagula, O. Pillai, V.B. Nair, P. Ramarao, Curr. Opin. Chem. Biol. 4 (2000) 468–473.
[68] H.D. Park, K.J. Lee, H.R. Yoon, H.H. Namb, Comput. Biol. Med. 35 (2005) 275–286.
[69] E. Tsalikian, R.W. Beck, W.V. Tamborlane, H.P. Chase, B.A. Buckingham, Diab. Care 27 (2004) 722–726.
[70] I.M.E. Wentholt, J.B.L. Hoekstra, A. Zwart, J.H. DeVries, Diabetologia 48 (2005) 1055–1058.
[71] A. Caduff, E. Hirt, Y. Feldman, Z. Ali, L. Heinemann, Biosens. Bioelectron. 19 (2003) 209–217.
[72] A. Pfutzner, A. Caduff, M. Larbig, T. Schrepfer, T. Forst, Diab. Technol. Ther. 6 (2004) 435–441.
[73] A. Caduff, F. Dewarrat, M. Talary, G. Stalder, L. Heinemann, Y. Feldman, Biosens. Bioelectron. 22 (2006) 598–604.
[74] D. Freger, A., Gal, A.M. Raykhman, US patent application, US 6954662 B2.
[75] I. Harman-Boehm, A. Gal, A.M. Raykhman, J.D. Zahn, E. Naidis, Y. Mayzel, J. Diab. Sci. Technol. 3 (2009) 253–260.
[76] R. Weiss, Y. Yegorchikov, A. Shusterman, I. Raz, Diab. Technol. Ther. 9 (2007) 68–74.
[77] http://www.c8-inc.com/us/press-release.html, 2012 (February 28).
[78] http://web.mit.edu/newsoffice/2010/glucose-monitor-0809.html, 2012 (January 14).
[79] I. Barman, C.-R. Kong, G.P. Singh, R.R. Dasari, M.S. Feld, Anal. Chem. 82 (2010) 6104–6114.
[80] http://blogs.umsl.edu/news/2011/03/29/glucose/, 2012 (January 14).
[81] B.P. Kovatchev, L.A. Gonder-Frederick, D.J. Cox, W.L. Clarke, Diab. Care 27 (2004) 1922–1928.
[82] W.L. Clarke, S. Anderson, L. Farhy, M. Breton, L. Gonder-Frederick, D. Cox, B. Kovatchev, Diab. Care 28 (2005) 2412–2417.
[83] D.C. Klonoff, Diab. Care 28 (2005) 1231–1239.
[84] D.D. Cunningham, J.A. Stenken (Eds.), In Vivo Glucose Sensing, John Wiley & Sons, Inc., New Jersey, 2010 (Chapter 1: Introduction to the glucose sensing problem).
[85] http://www.progical.com/, 2012 (January 14).