

Advancement and Challenges for Non-invasive Monitoring of Blood Glucose: A Review



Santu Guin and Madhurima Chattopadhyay

Abstract The aim of this study is to bring the current status as well as the future perspective of various techniques and devices for non-invasive monitoring of blood glucose. Blood glucose monitoring device is a very essential tool to assess the level of blood glucose frequently by diabetic patients as well as physicians. The most common commercialized method for blood glucose monitoring is invasive, painful, time-consuming, and expensive that requires finger pricking to draw the blood. To address this situation there is a need to develop a cost-effective noninvasive, reliable blood glucose monitoring device to improve the patient's daily life. In this context, several research articles have been studied. It has been observed that optical, thermal and electrical techniques are mainly adopted for noninvasive mode of blood glucose monitoring. Different types of spectroscopy techniques along with polarimetry and tomography are included in the optical method. Thermal emission spectroscopy and metabolic heat conformation are under thermal technique. Bioimpedance spectroscopy, electromagnetic sensing, reverse iontophoresis, millimeter, and micrometer wave sensing are included in the electrical technique. The general topology of different techniques/devices and challenges have been discussed over here.

Keywords Blood glucose monitoring · Diabetics · Non-invasive · Polarimetry · Tomography · Spectroscopy · Bioimpedance · Iontophoresis

1 Introduction

Diabetes Mellitus is a chronic, metabolic disorder that occurs when the human body becomes resistant to insulin or the pancreas is not able to make enough insulin. Currently, diabetes is the most common non-communicable disease and the World

S. Guin (✉)
Techno Main Salt Lake, Kolkata, India

M. Chattopadhyay
Heritage Institute of Technology, Kolkata, India
e-mail: madhurima.chattopadhyay@heritageit.edu

Health Organization (WHO) estimated about 422 million people had diabetes globally in 2014 (World Health Organization 2020). At the end of 2019, International Diabetes Federation (IDF) estimated that 463 million adults had diabetes and this number will increase to 700 million in 2045 (International Diabetes Federation 2019). This report also shows that India is the country with second-highest number of people (20–79 years) (77 million) living with type 2 diabetes worldwide next to China (International Diabetes Federation 2019). People with diabetes cannot properly metabolize glucose inside their body and typically pricking the fingertips by conventional glucose checking devices invasively to monitor their glucose levels (So et al. 2012). Therefore, non-invasive glucose monitoring devices overcome this painful experience by reducing the risk of infection and damage of finger tissues (So et al. 2012). Several techniques and devices for noninvasive monitoring of blood glucose have already been studied like in 1999, Khalil et al. (Khalil 1999) presented the glucose molecule and tissue properties at different wavelengths based on in-vivo and ex-vivo samples. Later in 2017, Lin et al. (2017) nicely reviewed some noninvasive devices as well as the main challenges related with glucose detection. In the same year, Chen et al. (2017) described the current scenario of the minimally invasive and noninvasive techniques for blood glucose measurement. Next year, Van Enter et al. (Van Enter and Von Hauff 2018) reviewed several properties of the glucose molecule and studied the effect on the accuracy of noninvasive techniques. Besides these, based on nanotechnology certain materials such as graphene, carbon nanotubes, etc. can also be used to develop a biosensor but they are still in early stage of research and development. A microneedle biosensor using Multiwall Carbon Nanotubes (MWCNTs) by amperometric method was developed by Jia et al. (2008). Later on, Zhigang et al. (2012) not only introduced the carbon nanotube and graphene based biosensors for glucose detection but also gave an outline of the current status with future perspective of these carbon nanomaterials. Afterwards, a carbon nanotube based transistor that is coated with pyrene-1-boronic acid molecules for glucose detection in saliva was developed by Lerner et al. (MIT 2020). Moreover, different synthetic materials like quantum dots, carbon nanotubes can be used in fluorescent technique to monitor parameters within a broad range of spectrum (Barone and Strano 2009). In this review, different techniques along with their advantages, limitations, and related devices have been considered. Various devices or companies for blood glucose sensing technology with their status as of December, 2019 are also listed here. Many of them are not commercially successful due to less sensitivity and low accuracy of the measurement (Tura et al. 2010). Some of the prototype devices are yet to be approved by the Food and Drug Administration (FDA) and the Communauté Européenne (CE).

2 Non-invasive Blood Glucose Monitoring Techniques

Based on the literature survey (So et al. 2012; Khalil 1999; Lin et al. 2017; Chen et al. 2017; Enter and Hauff 2018; Jia et al. 2008; Zhigang et al. 2012; MIT 2020;

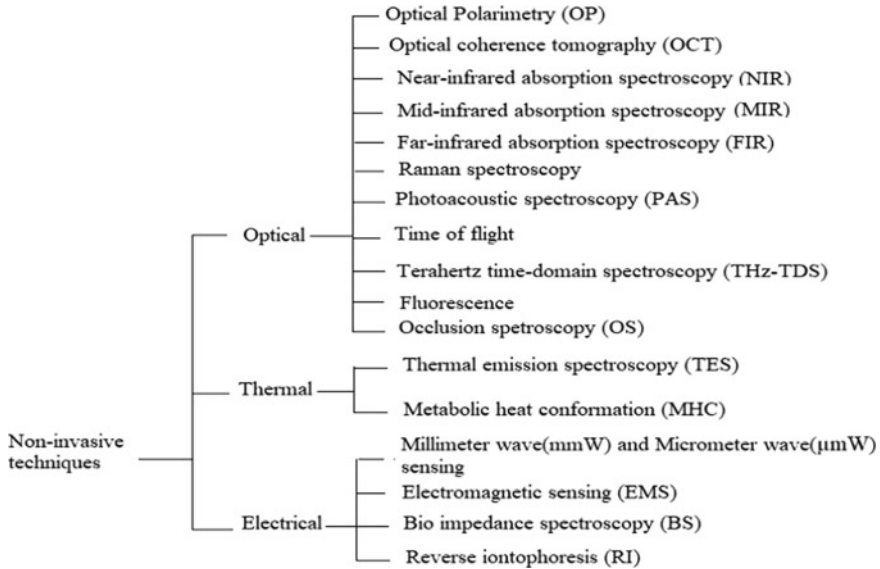


Fig. 1 Classification of non-invasive blood glucose monitoring techniques

Barone and Strano 2009; Tura et al. 2010; Malik and Coté 2010; Oliver et al. 2009; Lan et al. 2017; Coates 1998; Buchert 2004; Klonoff 1997; Cho et al. 2004; Shaker et al. 2018; Zhang et al. 2018; Potts et al. 2002a; Gourzi et al. 2005), it is found that several techniques like optical, thermal, and electrical have been used to monitor the blood glucose non-invasively as shown in Fig. 1. Basically optical technique uses the different properties of light like reflection, absorption and scattering when it passes through the biological media to interact with some molecules (Malik and Coté 2010; Oliver et al. 2009; Lan et al. 2017; Coates 1998). On the other hand, thermal techniques are based on the measurement of basal metabolic rates and heat generation by human body as it works in the far infrared region (Buchert 2004; Klonoff 1997; Cho et al. 2004). Another technique is electrical that is based on the detection of dielectric properties of glucose molecules using current, voltage, electromagnetic radiation, and ultrasound (Shaker et al. 2018; Zhang et al. 2018; Potts et al. 2002a; Gourzi et al. 2005).

2.1 Optical Polarimetry (OP)

This technique depends on the rotation of the plane of polarized light by the temperature, thickness, and concentrations of the solutes which is used to determine glucose levels in blood (Rawer et al. 2004; Gamessa 2019). This method is unaffected by pH variations but sensitive to temperature, motion and has poor system stability (Salam 2016).

2.2 Optical Coherence Tomography (OCT)

It is used to determine the glucose concentration present in blood by measuring the delay correlation between the scattered light from tissues in the sample arm and reflected light in the reference arm by employing an interferometer (Losoya et al. 2012). Hence, the refractive index increases in response to increase in glucose concentration causes a change in scattering coefficient which is used to detect the glucose concentration in blood. This technique generates high-resolution 2D image and has high in-depth scanning capability but is sensitive to motion and variations of skin temperature (Vashist 2012).

2.3 Near-Infrared (NIR) Spectroscopy

NIR spectroscopy uses a light beam in the range of 750–2500 nm wavelength which is focused on the body to measure the glucose concentration within tissues (Vashist 2012). It is simple, less expensive, has high signal-to-noise ratio (SNR), high in-depth tissue penetration, and availability of low-cost materials for commercial products but due to low glucose absorption capability as well as sensitive to physiological and environmental factors, it requires multivariate analysis (Tamar et al. 2017).

2.4 Mid Infrared (MIR) Spectroscopy

MIR spectroscopy uses spectrum in the range of 2.5–10 μm (Nawaz et al. 2016). As this method is considered only reflected and scattered light as no light is transmitted through the body, the response peaks of glucose are sharp compared to NIR spectrum but have drawbacks like poor penetration and strong water absorption (Coates 1998; Tamar et al. 2017; Nawaz et al. 2016).

2.5 Far Infrared (FIR) Spectroscopy

This technique is based on light absorption in the range of 1000 μm (at 0.3 THz frequency) and 10 μm (at 30 THz frequency) due to the molecule vibration and rotation of weak bonds and heavy atom bonds (Kalaiselvi et al. 2016). The quality of this technique is less scattered compared to NIR and MIR but has disadvantages like strong absorption of water and low-level power delivered by light source (Emilia et al. 2016).

2.6 Raman Spectroscopy

Raman spectroscopy is used to estimate glucose concentration in interstitial fluids by observing the emission of scattered light (Gonzales 2019). This emission is influenced by molecular vibration, rotation, and other low-frequency transitions. Using this technique, it is easy to separate signals compared to NIR as the resulting frequency bands are narrow and peaks are distinct in nature, low cost lasers are used and less sensitive to water and temperature changes but has limitations like laser intensity and wavelength is unstable, spectral acquisition time is long enough and low signal-to-noise ratio (Coates 1998).

2.7 Photoacoustic Spectroscopy (PAS)

It measures the light absorption and releases heat energy by generating photoacoustic pressure wave which is related with glucose concentration level (Anuj et al. 2013). This technique has higher sensitivity and poor photoacoustic response towards water. Therefore, it is expensive and also sensitive to physiological and environmental factors (Tura et al. 2007).

2.8 Time of Flight (TOF) and Terahertz Time-Domain Spectroscopy (THz-TDS)

TOF is based on the absorbed radiation of short laser pulses (few picoseconds) and travel time of photons through the sample. The pulse shape can be used to detect the glucose concentration in body fluid (Alarousu et al. 2003). This technique is immune to background noise and is possible to study of a broad frequency range with a single pulse but takes long measurement time having low spatial resolution (Gonzales 2019; Alarousu et al. 2003).

THz-TDS is based on reflection and scattering of short laser pulse in the time domain (few femtoseconds) to measure the travel time by the photons and absorption of the medium (Cherkasova et al. 2016). This technique has background noise immunity but has low penetration capability due to THz radiation as well as long measurement time having low spatial resolution.

2.9 Occlusion Spectroscopy

In this technique, a red or near infrared light is passed through a human finger after applying pressure that ceases the blood flow for few seconds. At the same time, the

transmitted and scattered light is detected by a detector that estimates the glucose concentration in blood (Uwadaira and Ikehata 2018). It has higher sensitivity as well as SNR but it needs compensation of signal drift (Nawaz et al. 2016).

2.10 Fluorescence

Fluorescence is based on the principle of fluorescent light emission at a particular wavelength. This technique uses a chemical compound fluorophores that keeps the track of glucose molecules in blood (Klonoff 1997). Fluorescence requires less calibration and has higher sensitivity towards glucose concentration. It is also immune to light scattering but it has short lifetime of fluorophore, biocompatibility issues and also depends on colour, pigmentation, thickness and potential toxicity to tissues (Gonzales 2019).

2.11 Thermal Emission Spectroscopy (TES)

It measures the naturally emitted infrared (IR) signals produced in the human body due to changes in the blood glucose concentration (Anuj et al. 2013; Tura et al. 2007). It has good reproducibility and does not require individual calibrations but has poor accuracy, sensitive to variation of body or tissue temperature and body movements (Buchert 2004).

2.12 Metabolic Heat Conformation (MHC)

This is involved with the measurement of physiological indices by mathematical analysis of thermal generation, hemoglobin (Hb), oxyhemoglobin (O₂Hb) and blood flow rate whose quantities are related with the glucose concentration by applying thermal, humidity, and optical sensors (Cho et al. 2004; Gonzales 2019). It is feasible and less expensive technique but suffers from strong interference of environmental conditions (Anuj et al. 2013).

2.13 Millimeter Wave (mmW) and Micrometer Wave (μmW)

As the millimeter and microwave radiation have lower energy photons and less scattering properties, it can be used to reach deeper position into the tissue with enough blood concentration (Shaker et al. 2018). It has high in-depth tissue penetration, no risk of ionization but sensitive to variations of physiological parameters like sweating,

breathing, and cardiac activities and has poor selectivity (Gonzales 2019; Anuj et al. 2013; Tura et al. 2007).

2.14 Electromagnetic Sensing (EMS)

In this technique, the variations in resonant frequency shift helps to detect blood's dielectric properties which relates with blood glucose concentration (Gamessa 2019; Salam 2016). It has no risk of ionization, minimize the interference from biological components in the tissue but highly sensitive to the temperature variations (Uwadaira and Ikehata 2018).

2.15 Bioimpedance Spectroscopy (BS)

This technique involves the measurement of impedance as a function of frequency by passing a small AC current of known intensity across a tissue. The changes in RBCs membrane potential are then determined by the dielectric spectrum in the range of 100 Hz–200 MHz (Oliver et al. 2009; Vashist 2012). It is a less expensive technique and does not require statistically-derived or population-specific prediction models but requires a calibration process in which the user must take rest for one hour at least before starting the measurements and sensitive to variation of physiological parameters (Gonzales 2019).

2.16 Reverse Iontophoresis (RI)

In reverse iontophoresis (RI), the migration of Na^+ and Cl^- ions from beneath the skin towards the cathode electrode and anode electrode, respectively create an electro-osmotic flow which makes the transport of glucose molecules are extracted through the epidermis. At the cathode there is a sensor measuring the glucose concentration by oxidization of glucose oxidase (GOx) (Frontino 2013). Here electrodes are easily placed on the skin and have good correlation between glucose level in the physiological fluid and blood but users feel skin irritation, itching and it is sensitive to variations of physiological plus environmental parameters (Potts et al. 2002b).

Summary of various devices or companies for blood glucose sensing technology with their status as of December, 2019 are listed in the following Table 1.

Table 1 Summarizes a list of devices or companies for blood glucose sensing technology with their status as of December, 2019

Device	Company	Technique used	Target area	Regulatory approvals and status
BioSensors	BioSensors, Inc.	Bioimpedance spectroscopy	Skin	Appeared in 2010 but still in R&D phase (So et al. 2012)
Optical glucose monitor™ system	C8 MediSensors, Inc.	Raman spectroscopy	Skin	CE mark approved in 2011. Until, 2012 it was used as an investigational device (So et al. 2012; Gonzales 2019; Tura et al. 2007)
Hitachi non-invasive blood sugar monitoring device	Hitachi Ltd.	Metabolic heat conformation	Fingertip skin	Pending approvals from FDA and the Japan Ministry of Health (Tura et al. 2007)
Diasensor® 1000	Biocontrol Technology, Inc.	Near infrared spectroscopy	Forearm skin	CE Mark approved in 2000. Discontinued in 2002 (Frontino 2013)
GlucoWatch® G2™ Biographer	Animas Corporation (Cygnus Inc. in Redwood City, California)	Reverse iontophoresis	Wrist skin	CE mark approved in 1999, FDA approved in 2001; (Potts et al. 2002b)
Diab-spot	DiagnOptics Technologies B.V.	Skin autofluorescence	Skin	CE mark approved in December, 2011 (SCOUT DS® and Diab-spot 2012)

(continued)

Table 1 (continued)

Device	Company	Technique used	Target area	Regulatory approvals and status
Pendra®	Biovotion AG (Pendragon Medical Ltd.)	Bioimpedance spectroscopy	Wrist skin	CE mark approved in 2003. Currently not available (Wentholt et al. 2005; Chen et al. 2018; DiCesare and Lakowicz 2001)
ClearPathDS-120	Freedom Meditech Inc.	Fluorescence technique	Eye	Appeared in 2005. CE mark in December 2013 (ClearPath DS-120 2014)
G2 Mobile	ESER Digital	Metabolic heat conformation	Fingertip skin	Unknown (Tang et al. 2011)
GlucoTrack™	Integrity Applications Ltd.	Combination of ultrasonic, electromagnetic sensing, and thermal	Ear lobe skin	Appeared in 2010. CE mark approved in 2013. Up to 2018, it was available in Asia and Europe (Tamar et al. 2018)
TensorTip Combo Glucometer (CoG)	Cnoga Medical, Israel	NIR spectroscopy	Fingertip skin	Appeared in 2010. CE mark approved in 2014. FDA approval is pending (Segman 2018)
TouchTrak Pro-200	Samsung Fine Chemicals Co. Ltd	Electromagnetic sensing	Fingertip skin	Appeared in 1999. But yet to be approved (Huzooree et al. 2018)
GlucoLight Sentris-100™ Monitor	GlucoLight Corporation	Optical coherence tomography	Skin dermis	First successful clinical trial was reported in 2007 (Huzooree et al. 2018)

3 Major Challenges for Non-invasive Blood Glucose Monitoring Devices

The major challenges in the development of non-invasive blood glucose monitoring devices are sensitivity, specificity, reliability, durability, responsiveness, efficiency, portability, and authenticity (Gonzales 2019). Most of the devices are suffering from the environmental and physiological factors such as temperature, pressure, humidity, light intensity, motion, sweating, blood perfusion, skin thickness, etc. which need to be removed (Anuj et al. 2013). High SNR is required to relate with blood glucose concentration and spectral response (Tura et al. 2007). It is very important to use different algorithms and multivariate statistical calibration models such as Artificial Neural Network (ANN), partial least squares (PLS), support vector machines (SVM), etc. in order to enhance the accuracy and reliability of the sensors and to improve the readability of the data (Tura et al. 2007). If the data set is linear, principal component analysis (PCA), partial least squares (PLS) and least absolute shrinkage and selection operator (LASSO) algorithms are efficient. However, if the data is non-linear in nature logistic regression (LR) and support vector machines (SVM) are efficient (Gonzales 2019; Tura et al. 2007). Another major aim is to reduce the calibration frequency against concurrent blood glucose values, which provides a detection of glucose concentration (Uwadaira and Ikehata 2018). In order to reach high efficacy, there is a need to develop such a system that should be stable with clinically reliable sensors to measure the glucose concentration with accuracy better than 15 mg/dl (0.8 mmol/lit) in the normal environment (Uwadaira and Ikehata. 2018; Frontino 2013). Another major issue is the physiological time lag between blood and tissue glucose that decreases the accuracy of the blood glucose monitoring (Oliver et al. 2009). Mostly infrared spectroscopy is widely used, but MHC can be feasible because of inexpensive equipment used in this method and clinical results provide a good correlation coefficient of 0.91 (Vashist 2012). Therefore, multisensory data fusion technology such as combinations of bio impedance, and NIR spectroscopy or MHC and NIR spectroscopy or dielectric spectroscopy and absorption spectroscopy can be implemented for the detection and compensation of additional parameters those are responsible for non-accuracy of the sensor (Tamar et al. 2017; Nawaz et al. 2016).

4 Conclusions

This study provides the current aspects and advancement in reliable, non-invasive blood glucose monitoring systems and also discusses the potential detection techniques used by the said device. These techniques can be broadly classified into optical, thermal and electrical where it is observed that the optical techniques are more efficient among the three because they do not require reference electrode and is free from electrical hazards as well as electromagnetic interference. Again, the acceptable skin depth penetration by the optical light source and the glucose molecule

which has clear optical absorption lines makes the optical technique more preferable. Also due to specific atomic bonding between carbon–oxygen–hydrogen in the glucose molecule which has definite vibration mode. This specific vibration mode enables identification of glucose molecule easily by an optical instrument.

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