A Review of Existing Non-invasive Techniques for Glucose Monitoring

Ammu Anna Mathew and S. Vivekanandan

Abstract Diabetes mellitus (DM) is a metabolic condition in where an increased blood sugar level over a prolonged period is observed. Diabetes can either be due to the inadequacy of insulin produced by the pancreas or due to improper response of the cell bodies to the insulin generated. The symptom of high blood sugar includes augmented hunger, increased thirst, and repeated urination. Diabetes may lead to several complications if left untreated. This paper deals with the latest accomplishments in non-invasive techniques for glucose and lifestyle observing which supports healthcare professionals in decision making. There are several procedures and techniques for analysis which can be put into two main categories—invasive procedures and non-invasive procedures. An invasive procedure is defined as a medical practice which pierces the skin in some manner whereas non-invasive procedure is any medical technique which does not pierce the skin. Non-invasive procedures are not always just good for making a diagnosis but sometimes they are used as treatment.

Keywords Lifestyle monitoring · Invasive techniques · Non-invasive techniques

1 Introduction

Diabetes mellitus, normally called as diabetes, is a set of diseases that depends on blood sugar (glucose) use in a person's body. The muscle and tissues cells are energized by glucose which plays a vital role in human health monitoring. The deficiency by the pancreas or cell response deficiency in insulin produced leads to diabetes.

The diabetes mellitus is classified into three main categories: Type 1 DM is the condition where due to loss of beta cells there is deficiency in insulin produced as a result of pancreas failure. This form was called as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes." The cell fails to respond to insulin produced at one stage leading to insulin resistance, and this is Type 2 DM. This form was

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referred to as “non-insulin-dependent diabetes mellitus” (NIDDM) or “adult-onset diabetes.” Inadequate exercise and obesity are the most common causes for this type of diabetes. Gestational diabetes is another form of diabetes found in pregnant women developing high blood sugar levels. These women may not have any previous history of diabetes.

A healthy diet, proper physical exercise, balanced body weight, and avoiding tobacco use can prevent and cure many diseases. Diabetic patients should take proper care of their foot and control their blood pressure. Type 1 DM should be treated with insulin injections. Type 2 DM can be handled with medications with or without insulin. Weight loss surgery for people with obesity is sometimes an effective measure in those with type 2 DM. After the birth of the baby, gestational diabetes usually gets resolved.

There are several procedures and techniques for glucose analysis. These procedures can be categorized as—invasive procedures, non-invasive procedures, and minimally invasive procedures. An invasive procedure is defined as a medical process which pierces the skin in some way but non-invasive procedures are medical procedures which does not break the skin. The non-invasive procedures followed are not always just good for making a diagnosis but also used as a treatment. Minimally invasive procedures enclose surgical techniques that limit the size of incisions needed and thereby reducing the wound healing time, associated pain and risk of infection [1].

2 Non-invasive Techniques

Non-invasive glucose monitoring indicates the measurement of blood glucose levels which is necessary for the diabetic people to avoid both prolonged and severe difficulties from the disease without sucking blood, piercing the skin, or causing any pain or trauma. Most commonly used non-invasive approaches are given below.

2.1 Near-Infrared Spectroscopy

Light waves with slightly larger wavelength than visible region are used for glucose measurement through skin. Near-infrared spectroscopy (NIRS) is a spectroscopic method which utilizes the near-infrared region in the electromagnetic spectrum ranging from 780 to 2500 nm. Near-infrared spectroscopy is built on the basis of molecular overtone and combination vibrations. The selection rules of quantum mechanics forbid such transitions. This results in a quite small molar absorptivity in the near-IR region. One advantage is that the penetration rate into a sample is more for NIR compared to mid-infrared radiation. There is no sample preparation or very little is done in near-infrared spectroscopy for bulk material penetration. A complex

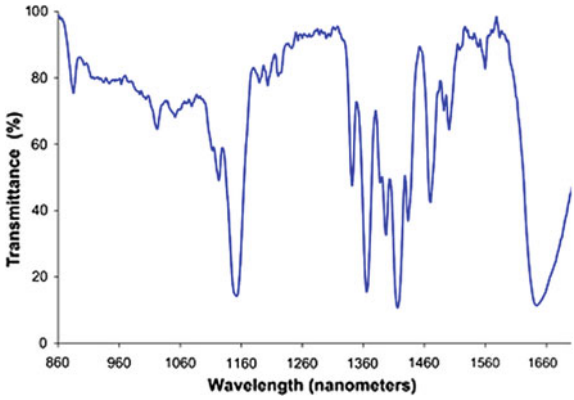

Fig. 1 Near-infrared spectroscopy (NIRS)

spectra is formed due to the molecular overtone and combination bands. The challenging part is the exact feature assignment to particular chemical components. The multiple variables calibration techniques like principal components analysis, partial least squares, and artificial neural networks are used to extract the desired chemical information. Figure 1 shows NIRS.

Near-infrared transmittance spectroscopy setup consisting of a light source and a detector placed on either side of the earlobe is used to measure the glucose across the earlobe during transmittance spectroscopy. The amount of near-infrared light passing through the earlobe is proportional to the amount of blood glucose in that region. The bone tissues absence and its relatively small thickness is one of the reasons to prefer earlobe. Near-infrared (NIR) light is applied on one side of the earlobe and a receiver is placed on the other side to receive the attenuated signal which is sampled and then processed. Two LEDs were used as the light source. An Indium gallium arsenide (InGaAs) photodiode having high response around a wavelength of 1550 nm was used. In addition, the output of the photodiode is connected with an RC low-pass filter to decrease the high-frequency noise.

2.2 Reverse Iontophoresis

Iontophoresis is the process of by which drug delivery is done through transdermal process for systematic distribution of active ingredients by developing a voltage gradient over the skin [2]. The electrophoresis and electroosmosis transport molecules across the stratum corneum. The permeability of the skin is increased by the electric field. An applied electric current constitutes active transport of matter directly and indirectly [3]. The unit of transport is mol/(cm^2*hour). The applications of iontophoresis include experimentation, therapy, and diagnosis. Figure 2 shows reverse iontophoresis.

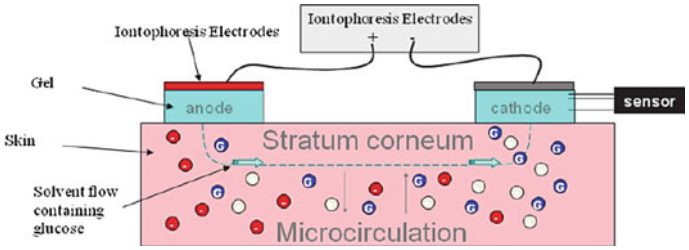

Fig. 2 Reverse iontophoresis

The detection and measurement of one or more small molecules, either intermittently or continuously, for example, glucose and lactate, in real time can be done through the transdermal patient observation technology called non-invasive reverse iontophoresis (RI). This technique works by extracting small molecules like glucose and lactate, from the patient skin using a gel electrode site on it. Glucose is pulled out through the skin using chemicals, electricity, or ultrasound in this approach [4–6].

There exists a relationship between the glucose concentrations in physiological fluid with that of blood glucose concentration. An advantage of this technology is that a physiologically appropriate fluid sample is collected with the help of electrodes which is then applied to the skin.

2.3 Optical Polarimetry

The electric field oscillates for light waves which can be planer, elliptical, or circular is called polarized light. Polarized light waves vibrate in a single plane. Equation (1) describes the phenomenon of polarimetry, where $[\alpha]$ is the specific rotation at a given wavelength (λ), α is the observed rotation, C is the concentration of optically active sample, and L is the sample path length.

$$[\alpha]_{\lambda} = \frac{\alpha}{CL} \tag{1}$$

Based on the above equation, the solute concentration considered is directly proportional to the observed spin of polarization. The optical active compound concentration can be calculated when the light beam passing through the sample in the observed polarization rotation is determined.

Here, estimation of the quantity of the polarized light that is pivoted by glucose in the front chamber of the eye containing the fluid humor is finished. The general sources of errors in this technique include eye movement and motion artifact. Figure 3 shows optical polarimetry.

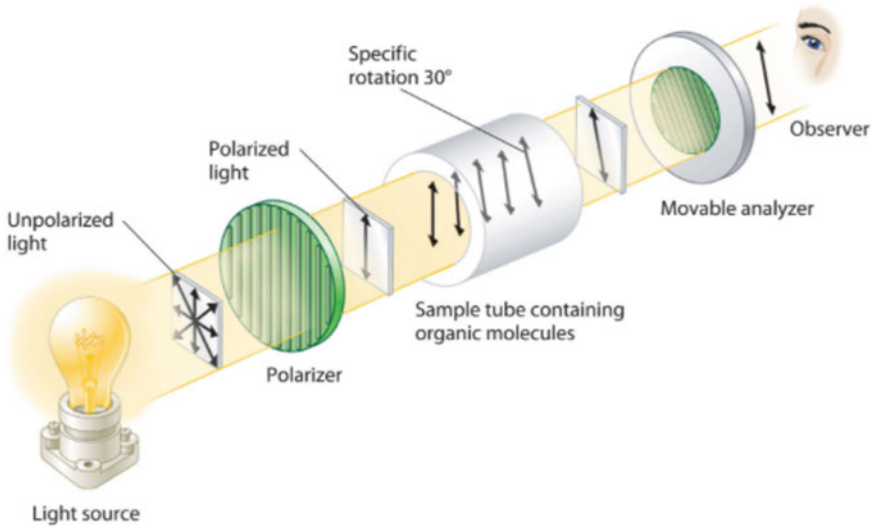

Fig. 3 Optical polarimetry

2.4 Bioimpedance Spectroscopy

The unoccupied glucokinase and glucose-bound glucokinase are differentiated from each other using this technology. The glucose binds glucokinase when considered there is a big change in the glucokinase conformation. There is a net electric dipole or charge in most of the proteins. An overall change in dipole movement of proteins occurs during the conformational movement of the protein in this method [7, 8]. The same is estimated using impedance biosensors where the impedance changes are delivered by authoritative of target particles to receptor atoms immobilized on the surface of microelectrodes [9] (Fig. 4).

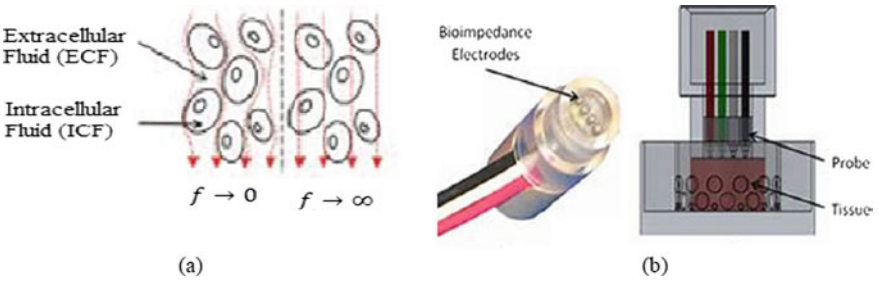

Fig. 4 Bioimpedance spectroscopy. **a** Principle. **b** Technology

Bioimpedance is a proportion of the resistance to denote the advancement of reagentless biosensors. The electric flow is moving through the tissues of a living creature. The estimation of bioelectrical impedance has demonstrated valuable as a non-obtrusive technique for estimating body organization. The utilization of measurably determined, populace explicit expectation models is not required in bioimpedance spectroscopy.

Separation between extracellular water and intracellular water is a potential value of this technique and, in this manner giving a gauge of body cell mass, hence portraying the blood bioimpedance properties. Contrasting with other existing gadgets this instrument is anything but difficult to utilize and low in cost.

2.5 Fluorescence Technology

Fluorophores are definite particles having the property of fluorescence, wherein they radiate a photon after not long retaining one with a higher-wavelength energy because of which an electron in the outer orbit of an atom will bounce from a ground-state orbital to an energized state orbital for which it requires a fixed amount of energy, which if there should be an occurrence of particles that assimilate light called chromophores. This can be gained by engrossing a photon with a strength equivalent or marginally higher. This is a short-lived state, and consequently the electron comes back to the ground-level orbital, losing the energy either as warmth or on account of fluorophores by transmitting a photon, which might be because of the loss of the distinction between energy of the assimilated photon and the necessary excitation energy, and will have a lower energy contrasted with the ingested photon, or, can be communicated as far as wavelength, for example, the discharged photon will have a more extended wavelength. The contrast between these two wavelengths is called Stokes' shift. Figure 5 shows fluorescence technology.

As indicated by an investigation, fluorescence of tears can be utilized for non-invasive glucose estimation as the glucose levels in tears correspond to the concentrations as in blood. As reported by Khalil, this methodology can be utilized to follow blood glucose with an estimated 30-minute lag time and does not experience the

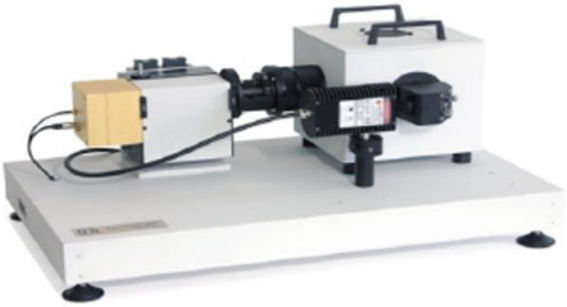

Fig. 5 Fluorescence technology

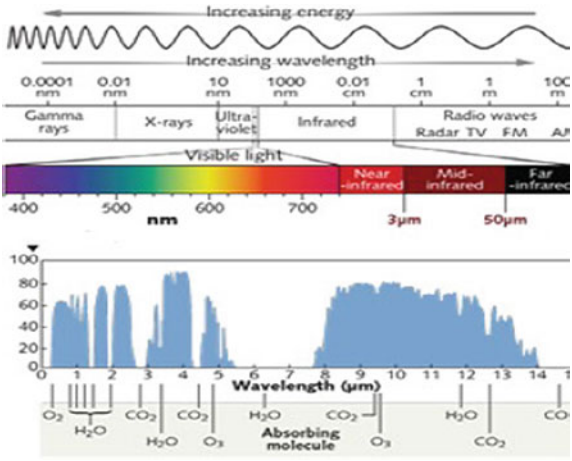

Fig. 6 Mid-infrared spectroscopy

ill effects of interference from variations in the light intensity of the encompassing condition [10].

2.6 Mid-Infrared Spectroscopy

Mid-infrared (MIR) spectroscopy principle is analogous to that of the infrared spectroscopy. The absorption measurement is done by placing the sample in MIR beam path of MIR frequency which is dependent on the light in the range of 2500–25,000 nm region of the spectrum. Absorption contrasts when MIR light hits the human tissues and can be shown by certain displaying methods in spectral quantitative investigation. For multivariate alignment for these constituents, a partial least squares calculation is commonly utilized. Figure 6 shows mid-infrared spectroscopy.

A decreased scattering phenomenon and an increased absorption are observed in MIR due to the high wavelength when compared with NIR spectroscopy. The response peaks of glucose and several other compounds appears to be more sharper in MIR spectroscopy while they are broad and weak in near-infrared spectroscopy [10] (Table 1).

2.7 Optical Coherence Tomography

A high-resolution imaging methodology which utilizes low-coherence interferometry (LCI) systems (in situ and real time) with the axial resolution of 1–15 m to perform high-resolution imaging of biological tissues, especially transparent tissue imaging up to depth of 2 mm, is called optical coherence tomography (OCT).

Table 1 Current non-invasive glucose monitoring device details

Device	Technology	Location on body	Frequency
Animas Technologies (Cygnus Inc.)	Reverse Iontophoresis	Wrist Skin	Continuous
Pendragon Medical (Switzerland)	Impedance Spectroscopy	Wrist Skin	Continuous
OrSense, NBM-200G (Israel)	Occlusion Spectroscopy	Fingertip Skin	Intermittent
C8 MediSensors (CA, USA)	Raman Spectroscopy	Abdomen Skin	Continuous
Integrity Applications, GlucoTrack (Israel)	Combination of Thermal, ultrasonic and electromagnetic	Earlobe tissue	Intermittent
Cnoga Medical, Combo Glucometer (Israel)	NIR Spectroscopy	Fingertip	Intermittent
Nemaura Medical SugarBEAT(UK)	Reverse Iontophoresis	Arm, leg, or abdomen	Continuous
MediWise GlucoWise (UK)	Radio wave spectroscopy	Earlobe skin or skin between the thumb and forefinger	Continuous

The tissue surface is scanned by moving the beam of light latterly over the sample for obtaining two-dimensional images having ultrahigh resolution [11]. Figure 7 shows Optical coherence tomography.

Depending on the utilization of a low coherence light, an optical signal acquisition method is developed with an interferometer having a reference arm and a sample arm, called optical coherence tomography. A reduction in the divergence between the sample and reference indices occurs as a result of the increase in interstitial fluid glucose concentration, which in turn increases the refractive index.

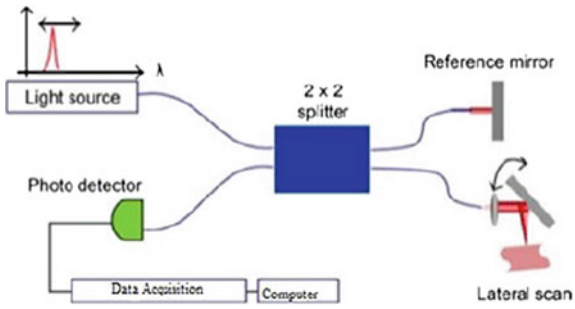

Fig. 7 Optical coherence tomography

2.8 Raman Spectroscopy

The observation of the low-frequency modes in a system in addition to the vibrational and rotational movements can be done through a spectroscopic technique called Raman spectroscopy. This technique is mainly utilized by researchers to identify the structural fingerprint thereby identifying the molecules present [12]. Figure 8 shows Raman spectroscopy.

This scattering technique corresponds to FTIR technique where a laser beam (usually 532 nm green laser) is directed onto the sample, resulting in the up and down movement of laser photon energy level and the scattered radiations are collected through a Peltier cooled detector. Mostly the scattered radiation has the same wave number as that of the incident laser beam but a fraction nearly 1×10^{-7} portion will be having a different wave number. This is the Raman signal.

When the sample interacts with a monochromatic radiation, this leads to reflection, absorption, or scattering. The change in wavelength of the scattered radiation gives the details about the sample molecular structure. This type of scattering is called Raman scattering and it is a weak process where the number of scattered photons is very small.

Scattered light from molecules has various components—the Rayleigh scatter and the Stokes and anti-Stokes Raman scatter. There is an observable change in the polarization along with its wavelength in all directions of the scattered radiation. The magnitude of the Raman effect can be related to polarization of the electrons in a molecule.

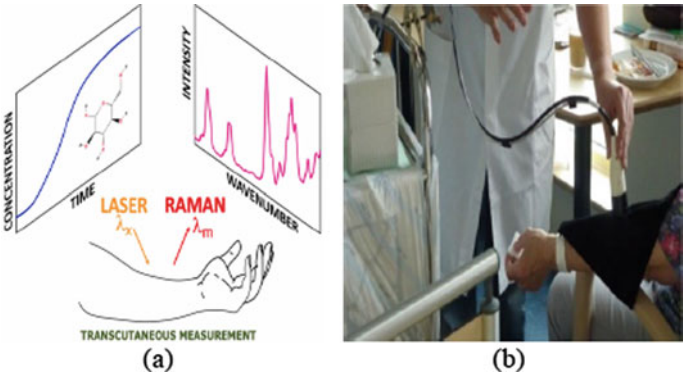

Fig. 8 Raman spectroscopy

Fig. 9 Ultrasound technology

2.9 Ultrasound Technology

The sound waves having frequencies above the upper audible range of human hearing is called ultrasounds. They are used to image the internal body parts. These waves have similar physical properties compared with normal audible sound with only exception that it is not received by humans. The limit of this signal varies from person to person, approximately in the range of 20 kilohertz in healthy young adults. The frequency range of operation for ultrasound devices is from 20 kHz up to several gigahertz. Figure 9 shows ultrasound technology.

Ultrasound finds several applications especially in the medical field like ultrasound imaging or sonography. Ultrasound is used to identify the objects and estimate the distances. They find invisible flaws during the non-destructive testing of products and structures.

Industrial application of ultrasound includes cleaning, mixing, and accelerating chemical processes. This technique is being experimented for using graphene diaphragms as a method of communication.

The photoacoustic response of blood, compared with water, can provide higher sensitivity in the determining the glucose compared to the traditional spectroscopy. Hence, the hydrocarbons and glucose distinguished easier [13].

2.9.1 Electromagnetic Sensing

In comparison with bioimpedance spectroscopy, this current technology decides the dielectric parameters of the blood. This technique depends on the electromagnetic coupling between the inductors whereas bioimpedance spectroscopy makes use of the electric current available for detection. The dielectric parameter variation in blood due to change in glucose concentration is analyzed using the electric current from sensor. The frequency range in this technique is 2.4–2.9 MHz. The efficacy of the device depends on the determination of this frequency [14] (Fig. 10).

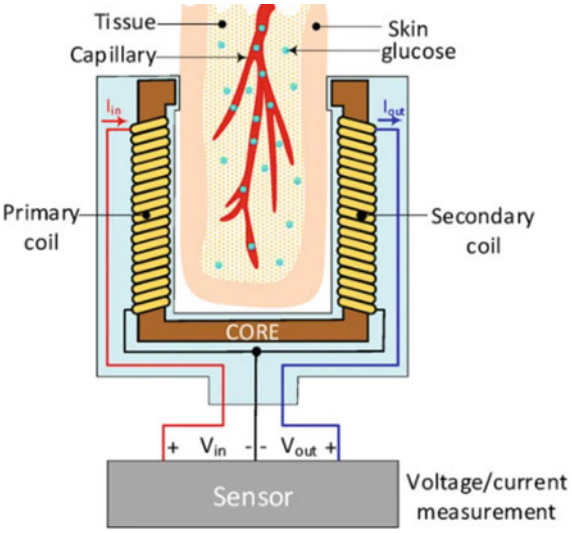

Fig. 10 Electromagnetic sensing technology

The impact of blood glucose can be separated by utilizing a specific frequency range and furthermore limits the characteristics of different substances like cholesterol can skew the measurements. In addition, as there is no ionization of the molecules of the body, it is moderately safe.

3 Advantages of Non-invasive Techniques

The merits of non-invasive techniques are (i) Pain-free: No finger pricking, no lancets require when making measurements, needle-free, no draw blood involve. (ii) User-friendly: easy to read data, big color touch screen: Easy to operate, clip onto the earlobe. (iii) No disposable: No more waste on test strips, lancets, and others.(iv) Self-diabetes management easier: Frequent monitoring can help diabetes patients see better and understand their glucose behavior over the time period. (v) History of data read are in tabular and graphic formats: Up to 1000 recent readings per user can see their trends over time. (vi) Long term of calibration validity: EarClip replace every 6 months, when replacing a new EarClip then do the calibration. (vii) Reduced lifecycle cost in long term: One-time expense with virtually unlimited measurements. Hence, it is preferable to select non-invasive technique over invasive techniques [15].

4 Conclusion

The predominance of diabetes is on the growth. People who are affected by Type 1 and Type 2 diabetes can live fuller, lengthier, and improved lives by wisely regulating their blood glucose levels. To do this completely, blood glucose levels must be organized on a systematic basis, in some cases as frequently as four or five times a day and more. Blood glucose level checking using invasive devices is both painful and costly. Lancet puncturing of the finger-tip to produce the requisite blood drop for testing causes pain. The expenditure comes from the replaceable test strips being inserted into a reader, on which the blood drop is employed. Thus, it is better to choose non-invasive techniques for glucose monitoring by replacing invasive techniques. It is advantageous to opt non-invasive techniques over invasive techniques in future.

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