Non-invasive sensing techniques for glucose detection: a review

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ABSTRACT

Diabetes is becoming more prevalent over the world, with approximately 7.8 million new cases diagnosed each year. The most crucial aspect of diabetes therapy is frequent glucose monitoring; the one and only way diabetics can maintain healthy blood sugar standard is through diet and exercise. Blood glucose monitoring techniques have gone through massive transformations over the past few years. Non-invasive procedures outperform invasive and minimally invasive ones in terms of inconvenience, pain, and recovery time. Thus, this review aims to explore the latest tools for non-invasive glucose monitoring sensors and techniques. The study showed that non-invasive techniques such as optical and non-optical techniques are better than invasive techniques in terms of accuracy, reliability, repeatability, and ease of use. The study also uncovered that the photoacoustic spectroscopy and ultrasonic techniques have room for further development and advancement considering their flexible nature. The work also proved that the ultrasonic technique is the most promising approach, in conclusion.

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1. INTRODUCTION

According to the World Health Organization (WHO), there are approximately 422 million people worldwide with diabetes [1]. If proper management and control are not applied, this number is expected to rise to 629 million by 2045 [2]. 1.6 million people die each year [1] as a result of diabetes, making it the seventh leading cause of death worldwide. Diabetes is a long-term metabolic disorder that impairs the body's ability to use food as fuel. Food we eat is typically turned into glucose (also known as sugar) and released into the bloodstream. The pancreas releases insulin when blood sugar levels rise. Insulin, a hormone made by the pancreas, helps the glucose found in food to get into the cells to be used for energy. In other words, insulin acts like a key to allow the glucose into the body's cells for the use of energy. In case of diabetes, either the pancreas is no longer able to produce the sufficient amount of insulin needed for the body or the body cannot make good use of the insulin it produces. As a result, too much blood glucose stays in the bloodstream. Consequently, complications of diabetes might develop, e.g., stroke, blindness, heart attack, and kidney failure.

Type 1 diabetes and type 2 diabetes are the two most common types of diabetes. type 1 diabetes (T1D) is characterized by the immune system attacking and killing the insulin-producing cells in the pancreas of the patient. People with diabetes who have this subtype account for approximately 10% of the population. A person can develop type 2 diabetes (T2D) or type 1 diabetes (T1D). Type 2 diabetes is the most common type of diabetes, and it is the most serious (T1D). Approximately 90% of diabetic patients have this type therefore the focus of this research is on this type. For the rest of their lives, individuals with type 1 and type 2 diabetes must keep a close eye on their blood sugar standards. A strict glucose monitor and control can help the patients in managing the symptoms, evaluating the therapy, and preventing or delaying the progression and complications of diabetes [3].

Blood glucose monitoring can be divided into invasive, minimally invasive, and non-invasive technologies, as shown in Figure 1. The invasive technologies require taking a small blood sample, whether that be through the use of a thin lancelet implanted transdermal or through the use of finger puncturing. On the other hand, the minimally invasive techniques aim to minimise the discomfort and invasiveness of the traditional invasive technologies. The non-invasive technologies eliminate the need for a blood sample, i.e., no need for bloodletting. Compared to the invasive and minimally invasive techniques, the non-invasive techniques overcome the limitations of invasiveness, pain, and time-consuming [4]. Thus, this review intends to give an up-to-date overview of the latest technologies for non-invasive glucose monitoring sensors and techniques.

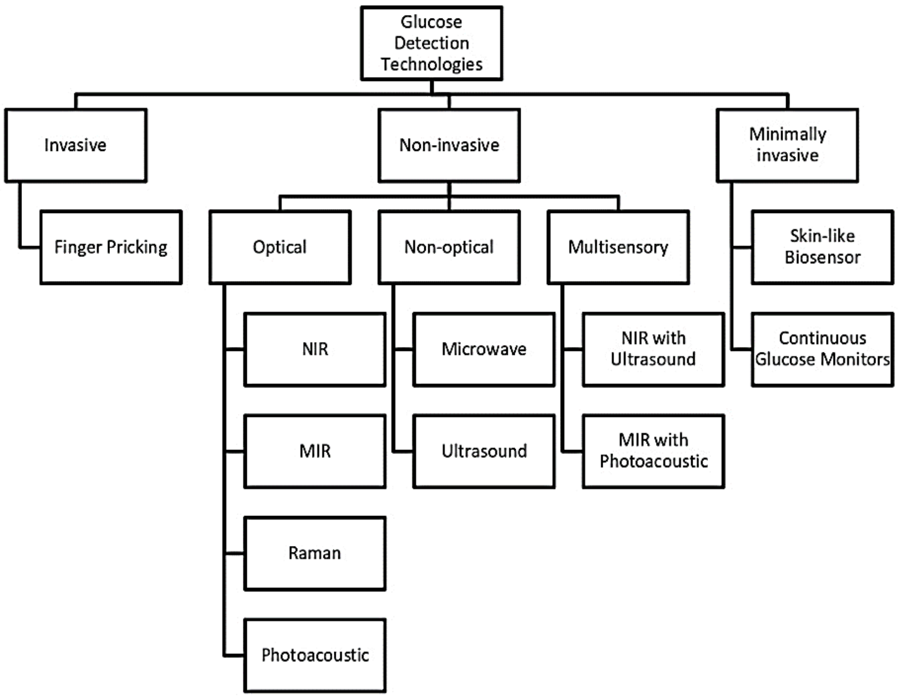

Figure 1. Summary of glucose detection technologies

2. OPTICAL TECHNIQUES

Optical techniques have received a lot of attention for non-invasive glucose monitoring. These techniques are considered as one of the most common non-invasive glucose detection and monitoring tools, since it does not require any withdraw of blood, which would allow comfort and safety for the diabetic while obtaining the glucose readings. The optical glucose sensor is, in general, an optical glucose sensor consists of a light source, a detector, and an optical transducer that converts detected light into a quantifiable electrical signal. They are primarily focused on glucose's intrinsic characteristics and rely on the use of opto-spectral bands to benefit of light's characteristics as it travels via living organisms. Through optical techniques, glucose concentration can be measured either directly using the interaction between light and glucose, or indirectly by measuring molecules that can reversibly bind to glucose, or by measuring the change in scattering properties in tissue as a function of glucose concentration [5]. This review will focus on four main optical techniques, which use the direct light-glucose interaction to measure glucose concentration. These four techniques are Near-infrared spectroscopy (NIRS), Mid-infrared spectroscopy (MIRS), Raman spectroscopy, and Photoacoustic spectroscopy (PAS). Each technique is discussed further down subsection.

Developing a reliable non-invasive glucose measuring device would be a life-changing issue for millions of diabetes worldwide. There are different types of non-invasive glucose monitors; optical, microwave, and ultrasonic techniques. The advantages and disadvantages of each method are summarised in Table 1.

Table 1. Summary of advantages and disadvantages of non-invasive glucose monitoring systems

Technique	Advantages	Disadvantages
Near-infrared Spectroscopy (NIRS)	– NIR signal band is water-transparent. – Low-cost material is required for high sensitivity of the photoconductive detectors	– Low wavelength range – Selectivity issues when determining glucose
Mid-infrared Spectroscopy (MIRS)	– Low scattering – In comparison to other spectroscopy methods, glucose exhibits the strongest absorption of MIR radiation – Absorption of water is very strong.	– Only reflection is possible because the depth of penetration is only just few micrometers. Too high of a wavelength range for some uses.
Raman Spectroscopy	– Appropriate for measuring scattered light on almost any surface, even those that are invisible• A high degree of specificity.	– Long collection time. Laser frequency and intensity instabilities
Photoacoustic Spectroscopy (PAS)	– Immune to water distortion. – Not influenced by scattering particles – Increased sensitivity runs under normal atmospheric pressure	– A high level of background noise – Longer time period for integrating the dataChangeable in temperature, pulsation and motion as well as ambient acoustics
Microwave Technique	– Ionization is not a concern. Highly responsive to variations in concentration of glucose. The signal penetrates deep enough to attain the intended glucose-containing tissue.	– Susceptible to biological difference – Poor selectivity
Ultrasonic Technique	– It is capable of penetrating deep into the skin or tissue and touring for long distances. Higher sensitivity than the rest of the techniques – There is a wide range of laser light frequencies that can be used.	– Affected by biological compounds, thermal gradients, and pressure shiftsCostly and highly susceptible to environmental changes, instruments
Glucose Remote Sensing Techniques	– It's flexible and biocompatible – Stable and accurate	– Excruciating sensor implantations. Data gaps caused by a lack of signals – Irritation of the skin and issue with the adhesive

2.1. Near-infrared spectroscopy

As one of the spectroscopic types of measurements, NIRS utilizes the infrared area of the electromagnetic spectrum (780 nm to 2,500 nm). Using NIRS, glucose levels can be measured under the skin to depths of few millimetres. NIRS is a promising and widely explored technique for the measurement of blood glucose. This technique is advanced due to its water transparency and relatively low cost. There are two measurement methods used for this technique: transmittance and reflectance [5].

A non-invasive blood glucose-measuring device, which was proposed by Luong *et al.* [6] continuously monitors blood glucose levels using infrared light 1550 nm to prevent the complications of diabetes. This device has the advantage of not requiring consumer supplies, so the cost would be lower than that of other similar devices. Additionally, it causes no pain and reduces infection complications. Cheng *et al.* [7] predicting blood glucose levels using near-infrared absorption can be enhanced by taking into account the human metabolic condition. A nonlinear autoregressive pattern with exogenous (NARX) input, seven initial input variables, and the sensitivity analysis method are used to to choose the major important factors for the NARX approach. As a result, the NARX model outperformed the other models in terms of prediction. A cheap and easy method that is discussed Manurung *et al.* [8] used a NIRS-based non-invasive blood glucose monitoring system. That was introduced to a number of diabetics who are less fortunate financially and have limited access to healthcare in Indonesia. The proposed system consists of a sensor that has a pair of LEDs and photodiodes that transmit and receive light with a wavelength of 940 nm. Then, the light intensity is transmitted to a smartphone application to convert it to blood glucose level. Non-invasive glucose monitoring techniques Li and Li [9] were developed using near-infrared light to tool up a painless and dependable tool for monitoring glucose. The method relies on detecting transmission laser power, which involves a semiconductor laser diode, S302C light power probe to recognize light beam, and PM100USB data transmission to the computer. Narkhede *et al.* [10] a near infrared light that is based on optical signals which uses LEDs emitting 940 nm wavelength signals. The fingertip sends optical signals, which are reflected by a phototransistor next to the LED, which detects blood glucose concentration based on the received signal's intensity. A technique called GluQo was used Rahmat *et al.* [11] where a near-infrared LED was placed on the fingertip to optically measure blood glucose concentration depending on the intensity of the received light, then it filters and amplifies the signal which will be sent to the microcontroller in order to display it on an LCD. The analysed voltage that is received indicates the glucose level of the blood. Xue *et al.* [12] a technique is shown that is based on rapid glucose measuring in skin tissue phantom by NIRS and Raman spectroscopy. Different methods were introduced in this technique, which are partial least squares (PLS) regression method, spectral region, spectral pre-treatment methods, and latent variables (LVs). A comparison between different NIRS methods with respect to overall accuracy and error percentage is shown in Table 2.

Table 2. Summary of the overall accuracy and error percentage of each individual method

Method	Reference	Accuracy	Error
Near-infrared Spectroscopy (NIRS)	7	CEG Zone A: 90.27% Zone B: 9.73%	N/A
	8	N/A	5.855 mg/dL
	11	N/A	7.20%
Mid-infrared Spectroscopy (MIRS)	17	N/A	Less than 20%
Raman Spectroscopy	19	CEG Zones A and B: 93.6%	N/A
	20	CEG Zones A and B: 93% MARD: 25.8%	N/A
	21	CEG Zones A and B: 100%	N/A
	22	CEG Zone A: 78.4% Zone B: 20.7%	N/A
Photoacoustic Spectroscopy	26	N/A	48 mg/dL
	30	MARD: 8.94%	14.95 mg/dL
Microwave Technique	35	90.6%	N/A
	37	N/A	12% (max)
	38	MARD: 12.5%	N/A
Ultrasound Technique	42	PEG Zone A: 94% MARD: 10.7%	N/A
	43	MARD: 26.6%	N/A
Glucose Remote Sensing Technique	47	CEG Zone A and B: 94-99% MARD: 13(6-22)%	N/A
	56	MARD: 16.7%	N/A

2.2. Mid-infrared spectroscopy

An infrared spectroscopic technique known as MIRS is one that uses a beam of light in the range between 2,500 and 10,000 nm and measures transmission and absorption. The required penetration depths for glucose detection are obtained using a quantum cascade laser (QCL), a semiconductor material divided into injecting and active regions [5]. Delbeck and Heise [13] presented their research based on a multivariate skin spectrum analysis. To achieve the largest selectivity for the development of non-invasive blood glucose method, they used the vibrational spectral fingerprint of glucose that is usually found in Mid-infrared spectroscopy. An integrating sphere Werth *et al.* [14] is used to promote a stable signal where it collects the backscattered light to be implemented, in order to achieve a more accurate glucose concentration prediction. Chen *et al.* [15] the authors in their work used wavelength ranges from (2.85 μm to 3.33 μm). They concluded that the relationship between the MIRS and the blood glucose could be applied to predict the actual blood glucose with some challenges that could affect the results. One of these challenges is body temperature. The study Reyes-Reyes *et al.* [16] explains the acetone concentration that is exhaled in the breath to detect the blood glucose by using the acetone signature with the quantum cascade laser based spectroscopic system. This study concluded that the acetone concentration in the breath of minors is different from those found in adults. Kottmann *et al.* [17] a study based on mid-infrared and photoacoustic detection is presented. The combination of the photoacoustic cell with the quantum cascade laser will boost the performance and stability. The result from the study was to have the measurement without involving extended wavelength ranges. A comparison between different MIRS methods with respect to overall accuracy and error percentage is shown in Table 2. In this appraisal, clark error grid (CEG) in zones A and B, mean absolute relative difference (MARD), and Parke’s error grid (PEG) were used in order to evaluate the accuracy of the compared methods. Each researcher has his own preferences in choosing which technique to use for the evaluation. The Raman spectroscopy technique is the most thoroughly investigated in terms of accuracy and error percentage while Mid-infrared spectroscopy technology is the weakest in term of its investigations.

2.3. Raman spectroscopy

When Sir Chandrasekhar Venkata Raman made his discovery in 1928, he discovered the Raman effect, which is used in Raman spectroscopy to determine how light is scattered. As there is no interaction between light and molecules, a photon doesn't lose any energy when it hits a molecular target. The scientific term for this phenomenon is "elastic scattering." In contrast, the molecules of the medium through which the light travels are capable of either absorbing or exchanging energy with photons. Consequently, the light particles' energy is bounced back and forth, which in turn influences the frequency. As a result, wavelengths change when frequencies do. It is called inelastic scattering in the scientific community. With such small amounts, the impact would be inconsequential. As a result, every medium has a distinct molecular scattering signature, which is determined by the number of molecules and their location within the medium. As a result of this, Raman spectroscopy, which is now used across a wide range of industries, was founded [18].

Pleus *et al.* [19] developed a system to prove the concept that demonstrates a practical realization of a Raman based non-invasive blood glucose measurement device. This research demonstrated that a Raman based non-invasive blood glucose measurement device can have performance comparable with early generation continuous glucose measurement systems. Lundsgaard-Nielsen *et al.* [20] the best measurement performance for glucose levels can be acquired from the base of the thumb above or below a depth of 250μm, below the skin's surface. This study demonstrated that Raman spectroscopy has performance on par with available invasive continuous glucose monitors and can be used for unsupervised home use. Li *et al.* [21] a new method of non-invasive blood glucose measurement instead of the commonly used interstitial fluid (ISF) is used in Raman. In this work, the author conducted an experiment and measured blood glucose from the microvessels in the superficial layer of the human nailfold. This method overcomes the time lag between the predicted blood glucose and the actual blood glucose from the ISF method. An experimental study was conducted Scholtes-Timmerman *et al.* [22] and a custom-made non-invasive Raman spectrometer system was proposed. The experiment was done on a hospitalized cohort of 111 subjects using advanced pre-processing and analysis algorithms. For correlating Raman data with blood glucose levels, blood glucose reference samples were used. Non-invasive, point-of-care glucose monitoring has made significant progress thanks to the development of this new system. Kang *et al.* [23] studied the molecular specificity of Raman spectroscopy. A statistical correlation with a reference glucose concentration was used in previous research on glucose sensing. Raman spectroscopy's usefulness in glucose sensing is called into question by these arguments because they fail to provide evidence of Raman peaks due to glucose concentration. As a non-invasive measurement technique, Raman spectroscopy has both advantages and disadvantages [24]. A fiber-optical probe, a Raman spectrometer, and a computer are all included in the gadget (microcontroller and smartphone). The device would make it easier to take regular readings for blood glucose monitoring. A comparison between different Raman spectroscopy methods with respect to overall accuracy and error percentage is shown in Table 2.

2.4. Photoacoustic spectroscopy

Using acoustic detection, a technique called PAS measures the influence of absorbed electromagnetic energy (particularly light) on matter. An expansion in temperature causes a sound wave or pressure wave because of the absorption of light energy. By using wavelengths of excitation, which are particularly absorbed by glucose, glucose concentrations of a sample can be identified through its photoacoustic response [25].

A differential continuous-wave photoacoustic spectroscopy (DCW-PAS) technique to obtain non-invasive blood glucose measurement is used Tanaka *et al.* [26]. DCW-PAS technique utilizes amplitude modulation of dual wavelengths of light to detect the changes in glucose concentration. A comparison of the obtained results using DCW-PAS with invasive techniques is done in this work to check the accuracy of the proposed method. The comparison showed a good agreement between the two different techniques (non-invasive and invasive). Tanaka *et al.* [27] two lights with different wavelengths that are amplitude-modulated to linearise the photoacoustic spectroscopy signal against glucose concentration are used. Additionally, the authors investigated the characteristics of PAS using a glucose aqueous solution. An in-vivo study of PAS was performed with healthy volunteers by attaching a PAS interface to the earlobe and monitoring the blood glucose levels. A comparison of PAS results with oral glucose test results has shown that there is tremendous potential for using PAS as a method of non-invasive blood glucose monitoring. Rassel *et al.* [28] focused on infrared spectroscopy techniques using a quantum cascade laser as an infrared light source for the detection of level of blood glucose in diabetic patients have been thoroughly reviewed and documented. Other researchers [29] focused on the development of a non-invasive blood glucose measurement tool using pulsed photoacoustic spectroscopy. Due to the system's design and implementation, it was possible to establish an exact mathematical correlation between the acoustic signal generated at the measurement site and the glucose levels. This study aims to introduce an effective, simple, portable, and safe method that reduces discomfort due to the measurement procedures. Measurements were made using a multi-wavelength photoacoustic measurement apparatus operating at 905 nm and 1,550 nm to obtain glucose workarounds with a concentration in the physiological range [30]. From the photoacoustic measurements, the amplitude and area-based features were used to determine the glucose concentration level. Photoacoustic signal intensity and peak position are studied Namita *et al.* [31]. This study's results indicate a linear relationship between the amplitude ratio and sugar concentration as well as a boost in signal intensity and sound speed for wavelengths with high light absorbance for glucose. A comparison between different Photoacoustic spectroscopy methods with respect to overall accuracy and error percentage is shown in Table 2.

3. MICROWAVE TECHNIQUE

The microwave technique has been widely used in the biomedical engineering field within recent years since it is a low-cost and high-resolution technique. The principle of microwave biosensors relies on the ability of electromagnetic fields to interact with matter differently depending on its structure, thus allowing the characterisation of tissues by analysing their dielectric properties in response to an applied excitation field. The ability of the microwave sensor to measure parameters inside a volume without damaging the sample makes them ideal for determining non-invasive measurement of physiological parameters of the human body such as blood glucose concentration [32].

Costanzo [33] the researchers discussed that the microwave relies on the different dielectric behaviour in the biological molecules as compared to air or water, thus changes in the wave propagation speed where it could be related to human tissues compositions. Xiao and Li [34] an ultra-wide band microwave to detect the blood glucose level was used. This approach is highly convenient and safe for patients. The time-frequency characteristics are utilized to examine the signals received. The validity of the method is proven by successfully getting a regularity of the energy of the signal received in the specific range, whereas the outcome was evaluated on a realistic earlobe. The results are verifying the capability of the method and it has good feasibility and robustness in measuring the blood glucose concentration. Other researchers used digital signal processing and artificial neural network to detect the blood glucose level through the human blood medium using the ultra-wide band (UWB) [35]. The system is user friendly and suitable for patients with an accuracy of detecting blood glucose about 90%. An inexpensive microwave resonator for measuring blood glucose levels in diabetics' fingers before and after meals was designed and simulated by Oloyo and Hu [36]. As low as this sensor detected 0.1g/l change, which is capable of distinguishing between glucose solutions with reflection coefficients ranging from 60 mg/dl to 110 mg/dl. Cebedio *et al.* [37] a microwave sensor, which is a part of a non-invasive blood glucose measurement device was proposed and designed. Three different microwave resonator structures, which are an open structure in which a finger of the patient is placed were analysed to fulfil the role of the sensor. The changes in blood glucose concentrations were translated to the resonance frequency. As a result, the sensor showed a satisfactory result with high sensitivity, stability, and repeatability. The microwave sensor to estimate blood glucose levels was used; this was done by a narrowband microstrip antenna that acts as a microwave sensor, and this band resonates at 1.3 GHz [38]. The narrowband senses blood glucose through the finger when the radiating patch interacts with the finger, and then it alters the electrical characteristics of the antenna in response to changes in glucose levels, resulting in a frequency shift. Baghbani *et al.* [39] a microstrip bandpass filter (non-invasive sensor) was proposed with cost-effectiveness, compact size, linearity, which can be used for diabetes patients to monitor their glucose levels continuously. Vrba *et al.* [40] researchers studied how to develop the microwave sensor by using the phantom. This phantom is used to simulate the blood glucose sample. The result from the phantom was to improve the accuracy of the sensor. Sathyanath *et al.* [41] the microwave method is considered a non-invasive blood glucose measurement. Many techniques of detecting glucose depend on the microwave principle. The first is the split ring resonator (SRR) and its complementary structure (CSRR), which work by monitoring the difference in resonance frequency of resonators as a function of the dielectric permittivity of the extracellular environment. This technique is considered as an efficient biosensor for the future. Xiao and Li [34] based their technique on an ultra-wide band (UWB) microwave detecting technique, which analyses the received ultraviolet B (UVB) microwave signals by the time-frequency features in order to determine the blood glucose levels non-invasively. Then, the reliability and sensitivity of the method are tested the results of which show that this method is highly sensitive and efficient. A comparison between different microwave techniques with respect to overall accuracy and error percentage is shown in Table 2.

4. ULTARSOUND TECHNIQUE

The term ultrasonic refers to sounds with frequencies exceeding 20 kHz. Ultrasound techniques could be combined with optical techniques like the near-infrared (NIR) or the mid-infrared (MIR) to form a stronger and more reliable reading. The major goal of the ultrasonic approach is to improve the withstanding optical technology by applying amplitude-modulated ultrasonic waves to improve measurements. Standing wave patterns in the blood medium cause molecular vibrations and oscillations. The velocity of sound through tissue can be used to examine differences in glucose level. The propagation velocity increases with glucose level. Because velocity profile is linearly related to glucose concentration, the faster an ultrasonic wave propagates through a tissue, the significantly quicker it promulgates [4].

NIRLUS® near infra-red light ultra sound (NIRLUS) Engineering AG, Lübeck, Germany) was evaluated under standard conditions was used to measure blood glucose Meyhöfer *et al.* [42]. An intravenous glucose tolerance test was done on 17 subjects with healthy bodies to measure blood glucose levels using NIRLUS and a "gold standard" laboratory reference system to compare the results between these two systems. As a result, the measurement using NIRLUS system was reproducible and accurate enough. Park *et al.* [43] an ultrasound-modulated optical sensing (UOS) technique was presented to monitor blood glucose non-invasively, and to avoid the severe complications of invasive methods. The system consists of an infrared laser (1645 nm) and a single-element focused ultrasound transducer that can localise diffused photons. The system has shown accurate results which give a good indication for great potential of the technique. Other researchers conducted a study using a 940 nm infrared light and a 40 kHz central frequency-dependent ultrasonic transmitter unit [44]. Human blood plasma mixed with Intralipid TM phantom samples was studied using modulated ultrasound and an infrared light-based technique to see how glucose-induced differences differed from those. Thirty people took part in the study, which used an oral glucose tolerance test and blood glucose checks at random, postprandial, and fasting stages. There were peak amplitudes in the Fast Fourier analysis of fasting, postprandial and random stages blood glucose tests for oral glucose tolerance tests. For mid-infrared spectroscopy, an ultrasonic standing wave that can generate reflection planes 100 nm below the surface of the sample was demonstrated Kitazaki *et al*. [45]. Due to the high compressibility of biological specimens, it is imperative that ultrasonic waves be attenuated when operating at these frequencies. As a result, an imaging-type Fourier spectrometer was used to successfully detect glucose absorbance inside an ultrasonic steady wave, thanks to the optical consistent tomography and generated parametric standing wave. A comparison between different ultrasonic techniques with respect to overall accuracy and error percentage is shown in Table 2.

5. GLUCOSE REMOTE SENSING TECHNIQUE

Using a commercial glucose remote sensor, which provides continuous glucose monitoring, this section describes briefly minimally invasive techniques for measuring glucose levels. A small sensor is inserted under the skin, usually on the belly or the arm, to facilitate this approach. As the name suggests, this sensor measures the amount of glucose present in the interstitium between cells. A transmitter wirelessly transmits the glucose readings from the sensor to a monitor every few minutes.We can achieve non-invasive blood glucose monitoring by replacing this minimally invasive sensor with one of the non-invasive sensors explained above. Thus, these commercial minimally invasive approaches are briefly discussed in this section as a first step toward converting minimally invasive systems into non-invasive systems.

A clinical investigation compared continuous glucose monitoring (CGM) with standard blood glucose monitoring to determine if CGM is more effective [46]. This investigation showed that CGM resulted in a small but statistically significant improvement in hypoglycaemia over 6 months compared with the standard blood glucose monitors. On the other hand, Zaharieva *et al.* [47] the delay between interstitial fluid and blood glucose measurement during aerobic exercises was studied. In this research, it has been shown that the drop in CGM lags behind the dip in blood glucose during prolonged aerobic exercise by 12 ± 11 min (mean $\pm$ standard deviation), and the mean absolute relative difference (MARD) rises to 13 (6–22) % [median (interquartile range)]. Thus, if hypoglycaemia is suspected during exercise this might be false positive and confirmation with a capillary glucose measurement is a must. Due to the research Bukara-Radujković *et al.* [48]. investigation of the effects of three months long continuous glucose monitoring in children with Type 1 diabetes using the iPro®2 CGM System is presented. Based on this study, metabolic control improved in children with diabetes after a 3-month period of using a CGM system. Omer *et al.* [49] a millimetre wave radar system in order to differentiate between blood samples that have different concentrations of glucose is proposed. It depends on remote detection of the glucose inside the tubes that contains blood samples due to the changes in the dielectric properties that share to a specific synthesis and composition. After that, a commercial coaxial probe kit has been developed in order to enhance the sensitivity, because it depends on detecting electromagnetic properties rather than the dielectric properties. This low-power portable system will be used daily by diabetics in the future. Fernández-Caramés *et al.* [50] enhanced the CGM system by adding some details to the design such as internet of things (IoT) capabilities to monitor diabetics remotely to avoid critical situations. This system collects glucose levels using smartphones, then it sends it to remote cloud, and storage is available in this system. Therefore, this system helps in controlling and raising global warnings of diabetes. Ramesh *et al*. [51] a remote patient monitoring system facilitates diagnosis and treatments for this dangerous disease (diabetes). This system depends on using smartphones and personal health devices. Moreover, in order to enhance the accuracy, sensitivity, and specificity in diabetes risk prediction a support vector machine was developed with a low-cost system. This enables doctors to make informed decisions. A disposable saliva nano-biosensor was proposed [52]. In this work, a low-cost device and continuous glucose monitoring is provided. The result was compared with a UV spectrophotometer.With the advancement of remote monitoring technologies, healthcare delivery and accessibility can be improved while remaining accessible, as explained in the review Vivekanandan and Devanand [53]. Latest studies have included the most recent advancements in remote monitoring technology. InDiaTel, a remote monitoring system for diabetic patients, was presented in a pilot research released in the first study [53]. Serial communication was established between the patient unit and the distant health professional units using a PIC microcontroller and multichannel information gathering. Because it is feasible and improves glycaemic control, more than 80% of the study participants agreed to use it. Lanzola *et al.* [54] a review of how remote monitoring systems have evolved over time is presented. This was done by describing the progress and the design of communication technologies and telemedicine systems for blood glucose monitoring. Furthermore, it discussed the challenges arising from sensors and actuators, and summarized the lessons learned. The standard ISO 15197:2013 guideline was used to evaluate the OneTouch Select® Plus blood glucose test system [55]. According to the evaluation, the system responded well to laboratory testing, meeting the ISO 15197:2013 requirements (i.e., precision, linearity, haematocrit, temperature, humidity, and altitude). Another study evaluated the accuracy and ease of use of the FreeStyle® libre flash glucose monitoring system (FGM) in children with type 1 diabetes mellitus [56]. The results showed an excellent correlation between FGM measurements and capillary blood glucose measurements. One thing to note about this system is that the wearing of the sensor requires special attention. A comparison between different glucose remote sensing techniques with respect to overall accuracy and error percentage is shown in Table 2.

6. THE MAIN CHALLENGES OF NON-INVASIVE GLUCOSE MONITORING

Developing non-invasive glucose sensors has been constrained by the measurement's indirect nature and an inevitable calibration procedure. Reducing accuracies, usability, and home-use applicability may necessitate a significant amount of effort to overcome [57]. Since the measured parameters can be affected by physiological factors other than glucose as well as external elements, non-invasive approaches have a low signal-to-noise ratio SNR because of their indirect nature. Non-invasive assays require an increase in the SNR, according to several reviews of past and current technologies. Non-invasive glucose monitoring devices typically have low sensitivity and specificity due to the low signal produced by glucose molecules [58], [59].

As a result of this physiological lag, indirect glucose monitoring has less precision. The measurement site and an individual's characteristics were shown to affect the time lag. A time lag may occur between measurements of blood glucose content in different parts of the body because non-invasive technologies use indirect estimations of glucose levels [60], [61]. Calibrating against blood glucose values provides an estimate of concentration because of the indirect nature of non-invasive measurements. Preliminary calibration is performed to reduce the influence of individual quasi-stable factors, such as tissue thickness and structure on the device [62].

Depending on the device and technology used, this procedure typically entails a series of paired invasive and non-invasive measurements performed at varying frequencies. Device usability and user satisfaction are expected to improve if the calibration process can be completed in a short and simple manner. The calibration process for the majority of non-invasive devices is lengthy and cumbersome [57], [58]. Another critical issue in the development of non-invasive devices is their suitability for home/office use, as manifested in simplicity and ultra-portability while taking a human factor approach. Unfortunately, most businesses provide only a limited amount of information on this subject [63]. Refering to Table 2 and [64], it is noticed that the average accuracy of the main non-invasive glucose monitoring methods is varied according to the used technique and can be summarized as shown in Table 3.

Table 3. Average accuracy of non-invasive glucose monitoring methods

Method	Average accuracy (%)
Near Infrared Spectroscopy	90
Raman Spectroscopy	83
Photoacostic Spectroscopy	71
Microwave	90.6
Ultrasound	94

7. CONCLUSION

An overview of the most recent technologies for glucose monitoring sensors and techniques, such as optical biosensors, has been provided in this review (near-infrared spectroscopy, mid-infrared spectroscopy, Raman spectroscopy and photoacoustic spectroscopy), microwave technique, and ultrasonic technique. It has also briefly discussed the commercial minimally invasive approaches as a first step toward converting minimally invasive systems into non-invasive systems. Several research attempts have been made in order to create an accurate measuring sensor with a simple way to monitor blood glucose. However, due to the difficulties involved, it will take immeasurable time with just a minor chance of success. Non-invasive, painless glucose monitoring will allow diabetics to check their blood glucose levels more frequently. However, more research is required to develop a non-invasive glucose monitoring system that can measure glucose with extreme precision. Wearable sensors may be useful in monitoring biomarkers for diabetes and other chronic diseases. There are non-invasive glucose monitoring devices now, which are already available in the consumer technology sector, can provide a knowledge base that can be spread to include disease monitoring or diagnostic tests, and have a meaningful effect on health and wellbeing worldwide. These non-invasive glucose-monitoring techniques are varying in their accuracy, simplicity, sensitivity, active wavelength, cost, temperature dependence, and other physical parameters depending on the using method.

According to the accuracy and the advantages of various non-invasive glucose monitoring techniques provided in this review, authors can conclude that the near infrared spectroscopy and ultrasonic techniques have room for further development and advancement considering their flexible nature, and that the ultrasonic technique is the most promising approach. To overcome the challenges mentioned in section 6, glucose monitoring technology presently needs significant developments, including faster reaction, interference reduction, and improved precision as well as better calibration, cost-effectiveness, comfort, and durability patient safety is paramount. Aside from that, the software and device features must be updated on a regular basis. Nonetheless, the developments glucose monitoring technology necessitates a significant amount of ongoing research and development. The improvements in non-invasive surveillance have, however, successfully laid the groundwork for various future diabetic screening applications.

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