Photoacoustic Spectroscopy Mediated Non-invasive Detection of Diabetics

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Abstract Day by day, the number of diabetic people is increasing worldwide. Since abnormal glucose levels in human blood cause diabetes, analysis of blood glucose concentrations is essential during diabetes therapy. Moreover, the existing glucose monitoring approaches commonly emphasize the invasive analysis method, which is generally time-consuming, painful, costly. Besides, these methods are prone to cause tissue damage. On the other hand, the non-invasive method of analysis overcomes this set of limitations. Different optical approaches have been used for the non-invasive detection of blood glucose levels. Interestingly, the photo-acoustic approach is one such technique that provides a high level of sensitivity during the method of analysis. Thus, this chapter introduces diabetics, followed by the importance of non-invasive technology compared to invasive technology. Further, it discusses the general principle of the photoacoustic spectroscopy and its application in monitoring glucose levels.

Keywords Photoacoustic spectroscopy · Glucose · Diabetes · Sensors · Non-invasive method · Blood

1 Introduction

Diabetes mellitus is a group of metabolic disorders identified by high blood sugar levels in the human body over a prolonged period and is well known as diabetes. However, diabetes occurs mainly in two instances, one where the pancreas secretes little insulin or no insulin at all and the other one where the insulin produced by the pancreas fails to work; this condition is known as the insulin resistance condition. The millions of cells in our body need food in an elementary form to make energy. When

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we consume food, our diet is broken down into basic sugar called glucose that supplies the body with the required energy for everyday activities. As the produced sugar cannot reach the cells, the insulin is released by the pancreas to act as a carrier and help the sugar reach into the cells and produce energy. Whenever the insulin fails to help this process, the sugar level in the blood increases dramatically. Eventually, it causes hyperglycemia, resulting in severe medical conditions such as kidney failure, tissue damage, blindness, heart disease, stroke, etc. Finally, it leads to death if left untreated [1]. The World Health Organization and International Diabetes Federation have addressed that diabetes is a primary concern affecting the world. Moreover, the current diabetes infection rate is around 382 million and is anticipated to reach approximately 592 million in 25 years [2–4]. Further, Cho et al. [4] mentioned that 451 million individuals were affected by diabetes in 2017. The patient numbers are likely to increase to more than 693 million by 2045 across the Globe [5].

There are two kinds of diabetes, *i.e.,* diabetes type 1 (sudden drop in glucose levels due to insufficient insulin production in the pancreas) and diabetes type 2 (high glucose levels due to ineffective use of insulin).

Diabetes type 1: The body's immune system is mainly responsible for fighting harmful foreign invaders like bacteria and viruses. Whereas, in people with diabetes type 1, the immune system attacks the insulin producing beta cells and destroys them in the pancreas. Thereby, the production of insulin stops in the body. Every 25 years, the prevalence of diabetes type 1 in children doubles [6, 7]. At present, the average loss of about 11–12 years of the life span was noted in the diabetes type 1 patients [8, 9]. Moreover, loss of life span is slightly higher in patients diagnosed before age 15 compared to those diagnosed after age 30 [9]. However, no therapeutic approach has been effective in preventing or curing diabetes type 1 [10, 11]. Since insulin is not produced in the body of patients who have diabetes type 1, insulin is regularly injected into their body, i.e., either by using injections insulin is injected into soft tissue, like the arm, buttocks, or stomach, numerous times per day or by using insulin pumps, which supply the insulin into the body via a small tube. In addition, blood sugar testing is essential to manage diabetes type 1, as glucose levels can go up and down quickly.

Diabetes type 2: This type of diabetes is caused by relative insulin deficiency because of beta-cell dysfunction [12–14]. Moreover, it frequently exists with insulin resistance. In all the cases of diabetes mellitus, 80% of the cases are of diabetes type 2. However, till today it remains an ill-defined type of disease. Also, there is no precise diagnostic criteria exist for diabetes type 2. Currently, 6 years were shortened in the life span due to diabetes type 2. However, it reaches 12 years in patients with diabetes type 2 at a younger age [15]. Several medications are available to treat diabetes type 2, but none of them has been proven to affect the progressive decline in beta-cell function over time significantly. RISE study on the patients with early diabetes type 2 revealed that function of beta cells was improved on treatment for 1 year with metformin, insulin plus metformin, or metformin plus GLP-1 analog. However, these positive effects vanished in 3 months when the treatment withdrawed [16]. Similar results were noted in the ACT NOW study, where the positive effects

of pioglitazone on beta-cell function is vanished after discontinuing the treatment [17, 18].

Both types of diabetes do not have an effective treatment, which means that regular monitoring of glucose in diabetic patients is essential for the rest of their lives. Numerous approaches have been developed to estimate glucose levels, including capacitive, coulometric, optical, enzymatic-electrochemical and non-enzymatic electrochemical [19–30].

Current measurement approaches are focused mainly on the invasive method, which uses the patient's blood. Most of the time, these technologies are expensive and may damage tissues. Moreover, these invasive approaches are always associated with a high risk of infection [31]. In contrast, various optical techniques have been available nowadays and used to monitor glucose levels in a non-invasive manner [32–34]. The main aim of these studies is to develop a technique with less pain and low infection risk. In these techniques, fingertips (where the interstitial fluid is present) are commonly used for measurement. Also, these measurements can be made by using a variety of natural areas, like saliva, earlobe, sweat. In this context, the photoacoustic approach emerged as one of the available non-invasive approaches, which is not affected by light scattering during the analysis and provides high sensitivity [31, 35].

2 History of Photoacoustic Spectroscopy

According to Rosencwaig, [36, 37] Tyndall, Rontgen, and Alexander Graham Bell, discovered the photoacoustic effect in 1881. Bell and Charles Summer Tainter were working together in the making of photophone. Further, Bell found that when modulated light irradiated on selenium (and other solid materials), it started to emit a sound and was attained by passing modulated light through a rotating disk with holes. Further, Bell used the spectrophotometer to study this phenomenon, and he noted that the intensity of emitted sound mainly depends on the wavelength of the incident light. Moreover, he attributed this observed sound effect to the optical absorption process [38].

However, the photoacoustic effect was applied in gas studies nearly after fifty years of its discovery. Since then, it has become a well-established method for analyzing gases, and the underlying concepts have been well understood [39]. On the other hand, Rosencwaig studied the photoacoustic effect in the field of solids after 90 years of its discovery. This delay was probably because of the unavailability of high-power light sources and sensitive sound detectors [40]. In particular, the 1st photoacoustic spectra acquired by Rosencwaig were on the materials like carbon-black, Cr_2O_3 crystal, and rhodamine-B powder [37]. Further, Rosencwaig has introduced photoacoustic spectroscopy technique as a new tool for solid research [40]. After this, he noted that photoacoustic spectroscopy allows similar spectra to be produced on any kind of semi-solid or solid system, whether it is amorphous, smear, gel, crystalline, etc.

In addition, since only the absorbed light converts into sound, the effect of light scattering on photoacoustic spectra is negligible [41].

Rosencwaig has also made a groundbreaking application of photoacoustic spectroscopy in the field of biology [40]. He recorded the photoacoustic spectra (200 to 800 nm) over many biological samples such as hemoglobin extracted from red blood cells, smears of whole blood, and plasma-free red blood cells. In addition, photoacoustic spectra (250 to 650 nm) of guinea pig epidermis were also obtained under different conditions. Also, he described the block diagram for the single-beam photoacoustic spectrometer comprising digital data acquisition. In 1980, Princeton Applied Research Corporation manufactured the 1st commercial spectrometer (Model 6001) [39, 42].

Moreover, dried solids comprising hemoproteins such as soluble proteins (cytochrome c) and insoluble or membrane-bound proteins (cytochrome P-450) were studied. Certain experiments have confirmed that this technique can determine the absorbing substances like some drugs in the dried urine samples (e.g., urine drops on filter paper) [42].

3 Conventional Methods of Glucose Monitoring

Diabetes mellitus has been named the "invisible killer" due to hypoglycemia and hyperglycemia [26]. Normal fasting blood glucose concentration level is around < 100 mg/dl (5.6 mmol/L), concentration level in between 100–125 mg/dL (5.6 to 6.9 mmol/L) is considered as prediabetes. Moreover, diabetes is higher than 126 mg/dL (7 mmol/L). However, glucose level concentration is less than 70 mg/dl (3.9 mmol/L) is termed hypoglycemia [19].

The glucose concentration level can be measured using serum, plasma, or whole blood. Although the serum or plasma samples were preferably chosen for analysis because the reading obtained using whole blood samples are typically has 15% lower values owing to the excess water content level in the blood cells. Intrinsically, traditional procedures for the analysis (invasive). At first, the glucose analysis was only possible in labs by using glucose's reducing property and condensation reactions. Still, it had some drawbacks, such as toxicity, cross-reaction, and non-specificity. Because of these drawbacks, this method was phased out from the clinical practices. Therefore, the latest approaches are based on enzymatic and hexokinase processes. Both processes have a specificity, high accuracy, and limited cross-reaction. Even though the laboratories use both processes, home testing and point-of-care use the enzymatic approach owing to its relative affordability and simplicity [1].

3.1 Invasive Methods of Glucose Monitoring

Most commercially available devices for continuous blood glucose measurement use electrochemical sensors due to their quick response for glucose detection in the blood and cost-effectiveness [43, 44]. Additionally, various commercially available devices use the lancets to prick the blood at the primary stage for monitoring blood glucose levels [45]. However, frequent monitoring (3–4 times in a day) via this process may cause panic and tissue damage attributable to the fingertip prickling to collect the blood sample [46]. Moreover, invasive methods are irritating and not recommended for continuous monitoring; they may also cause blood-related infections.

3.2 Minimally Invasive and Non-invasive Methods of Glucose Monitoring

Intensive research has been focused on non-invasive glucose detection systems because of the pain, risks, and discomfort associated with the conventional method of approach. Thus, it can be divided into two main groups: minimally invasive and non-invasive, detecting people with diabetes. Minimally invasive methods involve the extraction of somebody's fluid (e.g., interstitial fluid and tears) to quantify glucose concentrations via the enzyme reactions. Non-invasive methods entirely rely on some form of radiation, and it does not require any body fluids. Additionally, glucose monitoring systems can be divided into four sub-groups: electrical, thermal, optical, and nanotechnology [1].

Glucose monitoring in thermal methods includes identifying the physiological indices linked to the metabolic heat generation due to the glucose molecule, and it operates in the far-infrared region. In contrast, electronic methods generally involve analyzing the dielectric properties of the glucose molecules at lower frequencies by using electromagnetic radiation, ultrasound, and current. In a general context, the optical method includes all the techniques developed to operate in the ultraviolet and optical spectrum bands because they take advantage of the reflective, absorbing, and dispersing properties of light while transmitting through biological media. Additionally, there is a new area called nanotechnology for glucose monitoring. Presently, only two methods have started exploring this area extensively (surface plasmon resonance and fluorescence), along with optical methods. Nevertheless, various possible methods can be established, such as plasmonic and carbon nanotubes [47–50]. However, they are still at a very early stage of growth, and most of their present advancements are being made on the theoretical side. However, it is worth noting that most of these techniques are focused on minimizing noting that most of these techniques are focused on minimizing their impact physiological variability and the diverse environmental factors irrespective of the form of the technology used during the time analysis [1].

4 Theory of Photoacoustic Spectroscopy

Usually, when a substance absorbs light, there are several paths that energy can go. As shown by Eq. 1, light is always conserved,

$$1 = A + T + R \tag{1}$$

where

A—Absorbance

T—Transmittance

R—Reflectance.

The light that hits the sample must either be absorbed or transmitted through the material or reflected off the material. Photoacoustic spectroscopy relies on the absorbed path of light since it releases heat. As the light strikes the sample, the photons are absorbed, and the electrons are excited. This energy was further released as heat, and acoustic waves were formed as the heat expanded. The process is shown in Fig. 1.

Electrons are excited either vibrationally or electronically as light is absorbed. Electrons move to a higher energy level in the case of electrical excitation. As they fall back to their original state, i.e., ground state, the extra energy is released as heat. Another form of heat generation is via the collisional deactivation process, which involves atom's collision. The collision of atoms produces energy in the form of heat. Even so, in the case of electronic excitation, energy can also be dissipated by radiative emissions or chemical reactions, as described in Fig. 1. The energy emits photons in the radiative emission process, making it useless for photoacoustic spectroscopy (that needs heat). This process decreases the amount of heat formed because energy is spent elsewhere. Chemical reactions in heat can occur, but only part of the absorbed energy goes to heat.

But on the other hand, radiative emissions and chemical reactions have little impact on vibrational energy. The vibration's lifetime is long enough to avoid interferences because of the chemical reactions and radiative emissions. The atoms thus have as much time as required to execute the collision deactivation process, which efficiently uses the entire amount of energy for heat transfer.

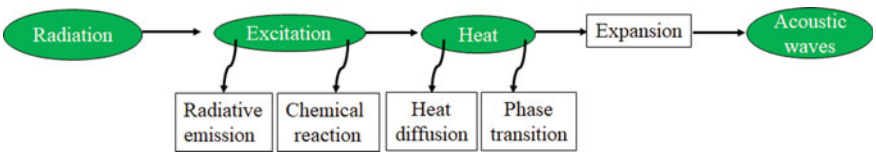

Fig. 1 Schematic illustration for the generation of acoustic waves

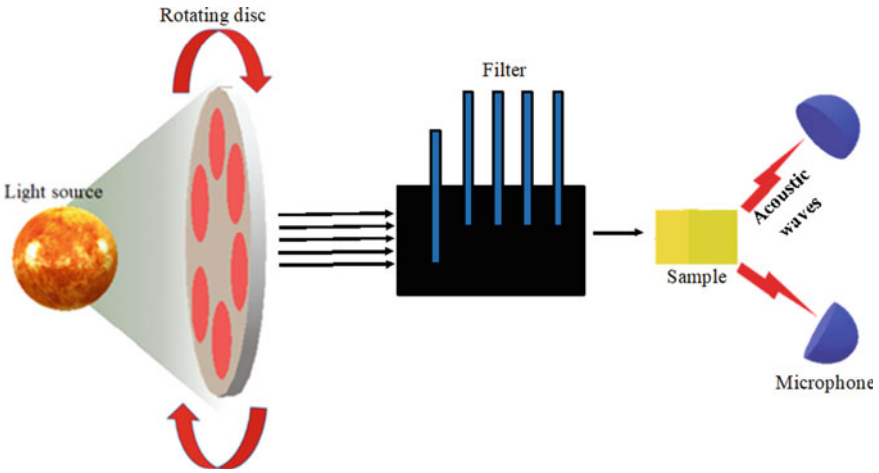

Fig. 2 Primary components of the photoacoustic spectrometer

The thermal expansion also occurs with the formation of heat. The expansion of heat produces localized pressure waves which can be analyzed as acoustic waves. Nevertheless, as in the case of energy formation, heat may also be lost through the environment. Heat diffusion decreases the temperature across the emitted energy source, which reduces the pressure fields. When acoustic waves are sent after each pulse of light, the sensor will analyze those waves. Similarly, each pulse of light will change the frequency of each pulse of light, and the produced acoustic wave will be analyzed and plotted as a spectrum pertained to a sample material.

Due to the tremendous technological advancement in recent years, technological development in amplifiers, light sources, and sensors has advanced dramatically. Figure 2 depicts a schematic configuration inside a photoacoustic spectrometer. Usually, light sources use infrared lasers or wire filaments such as tungsten that emit high light intensity. To give the pulses of light to the sample, the light source is either switched off or switched on to create the pulsing effect or the spinning disk with the openings to monitor the pulses of light passing through it. Further, the mirror channels the waves of light to a series of filters, which can be modified to adjust the wavelength of the light entering the sample. If the light goes through the filter, it reaches the contact window, where the sample is placed. Moreover, two microphones are mounted inside to collect the acoustic waves and sent to monitor the formed electrical signal. Similarly, various wavelengths are examined, and a sample spectrum is produced.

5 Recent Advancement in Photoacoustic Spectroscopy for the Detection of Glucose

A photoacoustic sensor based on an external cavity diode laser and a cheap piezoelectric film transducer for the glucose analysis has been shown by Bayrakli et al. [31] Further, the laser operation was shown to be amplitude-stabilized single mode. Additionally, a 9 GHz range of fine-tuning was reached using this setup. Moreover, they used a PVDF-based piezoelectric film transducer as a detector that produces the electrical signal concerning the acoustic signals obtained by the glucose molecules after absorbing the laser beam. They observed the detection limit of about 50 mM (900 mg/dl) for the analyzed samples. Finally, they concluded that these sensor's sensitivity could be improved to detect glucose concentration levels in the interstitial fluid below the skin. Additionally, they stated that reduced noise levels and the enhanced acoustic signal could be obtained by improving the laser quality and finding effective photoacoustic resonators with different geometries in the future.

A near-infrared (NIR) optoacoustic spectrometer is used by Ghazaryan et al. [51] to detect physiological glucose concentrations in the aqueous phase, it provided the glucose spectra between 850 and 1900 nm and measured at the multiple concentration ranges. Additionally, they implemented the dictionary learning and ratio metric techniques with a training data set. They validated their application for the measurement of glucose concentration with optoacoustic in the data set of the probe. Further, the authors noted the superior signal-to-noise ratio for the dictionary learning method compared to the ratio metric method over a wide range of glucose concentrations. Moreover, they observed the linear relationship between the concentration of physiological glucose and the intensity of the optoacoustic signal. The results are in line with the findings of optical spectroscopy. Therefore, they described physiological glucose concentration monitoring efficacy via NIR optoacoustic spectroscopy, which allowed the glucose-sensing with a precision of $\pm$ 10 mg/dl.

For the first time, Dasa et al. [52] designed a supercontinuum laser-based multispectral photoacoustic sensing system, and they used it to monitor cholesterol and glucose in the wavelength around 1540–1840 nm (first overtone region). Additionally, they demonstrated how this designed system could recognize the absorption properties of different analytes and then choose an acceptable wavelength range for further analysis. Moreover, they performed a simple ratiometric analysis and demonstrated the viability of this system for reliable glucose monitoring over a wide variety of concentrations. Furthermore, this study varied the concentrations from 0-8 g/dL, covering the commonly encountering glucose concentrations inside the human body (0-400 mg/dL). Previous studies [51, 53, 54] revealed that the photoacoustic signal linearly varies with the glucose concentration; hence, they also performed the linear regression examination to predict different glucose concentration levels with clinically acceptable accuracy concerning the standard Clarke error grid analysis. Results revealed that this system could be used as label-free and non-invasive continuous glucose monitoring.

Kottmann et al. [33] proposed a photoacoustic system composed of a mid-infrared quantum cascade laser used to monitor glucose present in the human tissue. That study used the fiber-based quantum cascade laser-photoacoustic framework and the new dual quantum cascade laser-photoacoustic set-up. Unlike traditional methods, this approach is entirely non-invasive. It does not record blood glucose concentration directly but the glucose concentration level in the interstitial fluid. However, it is related to the blood glucose level with a delay time of $\leq$ 15 min at the measurement sites. In addition, the authors analyzed the efficacy of an oral glucose tolerance test for healthy individuals. They conducted tests with the photoacoustic cell by closely contacting the forearm to obtain continuous monitoring results for about 90 min. At the same time, blood glucose concentrations were assessed by fingertips every 10 min, and blood glucose levels were measured from the glucometer. The findings suggested that the approach with a single quantum cascade laser produces positive results but does not always have a definite correlation with the blood glucose measurement data from the glucometer. The dual-wavelength protocol substantially increases the measurement stability, and the blood glucose level instability of $\pm$ 30 mg/dL is obtained at a confidence level of about 90%. The authors concluded that detection sensitivity could be increased by using higher laser power up to the permissible exposure level for short-term irradiation. It should be stressed that no specialized data treatment, such as the principal component evaluation comprising the entire wavelength tuning ranges, has been implemented to show viability under practical circumstances, i.e., for continuous individual measurements. In addition, more progress is required from the experiments involving more than two wavelengths characteristic of glucose absorption, involving many quantum cascade lasers or even a quantum cascade laser array of pre-selected fixed wavelengths. Finally, the authors stated that experiments on diabetic patients need to be carried out to assess the efficacy and to determine the potential of their designed diagnostic method.

To improve the detection sensitivity of the photoacoustic method, a measurable depth of the blood glucose concentration level was experimentally identified by Wadamori et al. [55] Here, the measurable depth of the photoacoustic spectroscopy mainly depends on the modulation frequency of the chopped light falling on the sample. Further, they established a relationship between the thickness of the sample and the used modulation frequency. During this set of experiments, the authors utilized the photoacoustic detector composed of an acoustic resonance pipe, and an optical microphone and a two-layer model consisting of sheets of silicone with different optical absorption properties. Furthermore, they noted the measurable depth around 2–3 mm in these experiments with a 1000–2000 Hz modulation frequency. In addition, they discussed theoretically the reason for the measurable depth to be more profound when compared to the sample's thermal diffusion length. In addition, these thermoelastic wave analyses clarified the relationship between the observable depth in a tissue and the propagation of the photoacoustic signal.

Photoacoustic technique comprising of tunable pulsed laser for glucose level detection was presented by Ren et al [56]. This set-up used the light source (532 nm pumped Nd: YAG optical parametric oscillator pulsed laser) for excitation and acoustic signal detector (confocal PZT transducer). Further, the authors prepared

the various concentrated solutions of glucose. It was further loaded into the quartz cuvette, then irradiated with a laser beam, and obtained the time-resolved photoacoustic signals with an average of 512 times. Furthermore, the authors received the photoacoustic peak to peak values from the wavelength range from 1300 to 2300 nm (near-infrared spectral range) for all glucose solutions. Moreover, the authors used the variance and one-order derivative spectral strategy in four photoacoustic peaks to peak signals to determine the typical glucose wavelengths. Eventually, the authors used the least square fitting algorithm to adjust the photoacoustic peak to peak values and the corresponding glucose concentration levels to obtain the optimal typical glucose wavelengths. The expected concentrations were determined by using the least square fitting algorithm. The estimated error in concentration was all less than 0.62 mmol/dl.

Pai et al. demonstrated the use of near-infrared photoacoustic spectroscopy for continuous non-invasive glucose analysis [57]. They designed a different photoacoustic measuring system, and photoacoustic observations were performed for glucose samples at various excitation wavelengths in the near-infrared region. A variety of frequency and time domain characteristics and amplitude and area-based characteristics were obtained using photoacoustic analysis. The authors noted that these properties were proportional to the glucose content of the sample, and they obtained similar results for the photoacoustic tests of whole blood samples at various glucose concentrations. Consequently, in vivo photoacoustic tests were calibrated using a quadratic fit on a cohort of 30 volunteers and further compared the obtained results with the reference glucose levels. The experiments were performed using a standard blood glucose meter. The authors performed a comparison of 196 measurement pairs of predicted and reference glucose level concentrations using the Clarke Error Grid. The result exhibited a point distribution of 87.24% and 12.76% over zones A and B, with no measurement pairs dropping in inappropriate zones C, D, and E of the error grid. Also, the authors observed the expected mean absolute difference of about 12.57 $\pm$ 13.90 mg/dl and the mean absolute relative difference of about 9.61 $\pm$ 10.55%.

Sim et al. [58] proposed a strategy to overcome the problems of non-invasive measures of glucose by increasing the reliability of micrometer-scale detection. Before spectroscopic measurement, authors collected the skin's microscopic spatial details from the same laser used for spectroscopic analysis. The authors noted the inhomogeneity in the microscopic image of the fingertip skin with a mid-infrared laser; this observation was attributed to the secretion from the eccrine sweat glands that greatly influenced the mid-infrared spectra. Further, they selected the intact positions where the secretion products were barely intrusive; hence, temporal and spatial heterogeneity were reduced. Numerous attempts have been made for many decades to design non-invasive methods of detecting glucose. However, due to the skin secretion materials, the repeatability and accuracy are still below compared to those of the invasive methods. Finally, the authors stated that their strategy has tremendous potential to build such a technology to overcome these long-standing problems.

6 Advantages of Photoacoustic Spectroscopy

Some of the advantages of photoacoustic spectroscopy are listed below, [1]

- This method is relatively simple.
- Not susceptible to the sensing of sodium chloride, albumin, and cholesterol.
- Scattering particles are not influencing the photoacoustic signal.

7 Disadvantages of Photoacoustic Spectroscopy

Some of the disadvantages of photoacoustic spectroscopy are listed below, [1]

- This approach is sensitive to variations caused by motion, pulsation, acoustic noise, and temperature.
- It requires a long integration time.
- It has a low signal-to-noise ratio.

8 Future Outlook

Photoacoustic spectroscopy has the potential for efficient glucose measurement in the blood shortly as the non-invasive method if extensive research works are carried to produce the devices with the following properties.

- The device should produce a wide range of glucose measurements of about 30–600 mg/dl,
- User friendly, portable, and durable device,
- A device with a borderline cross indication
- Low cost.

9 Conclusion

This book chapter started with the introduction to people with diabetes, followed by the history of photoacoustic spectroscopy. Further, the conventional methods for glucose monitoring and minimally invasive and non-invasive methods have been discussed. Furthermore, the theory behind photoacoustic spectroscopy instruments and the recent advancements of photoacoustic spectroscopy for detecting glucose and their advantages and disadvantages have been covered in detail. The commonly used sources of light, wavelength region, and the detectors in glucose detection setup based on photoacoustic spectra are described in Table 1. At present, low specificity, low sensitivity and interference are the main hindrances in the measurement of non-invasive blood glucose levels due to the various imperfections noted in the utilized

Table 1 Various types of sources, wavelength regions, and the detectors used for the glucose detection using photoacoustic spectra

Source	Wavelength (nm)	Detector	References
High energy supercontinuum laser	1500–1900	Ultrasonic transducer	[52]
External cavity quantum cascade laser	8000–11,111	Ultrasound transducer	[58]
Continuous-wave quantum cascade laser	9090–9950	Miniature electret microphone	[33]
Two pulsed laser diodes	905 and 1550	Piezoelectric transducer (Lead Zirconate Titanate)	[57]
Laser diode	1550	Microphone	[55]
532 nm pumped Nd: YAG optical parametric oscillator pulsed laser	600-2500 nm	PZT ultrasonic transducer	[56]
External cavity diode laser	1050–1700	Piezo transducer (polyvinylidene fluoride)	[31]
Optical parametric oscillator laser	850–1900	Ultrasound detector	[51]

software and hardware components. However, the rapid changes in technological advancement and the further advance in the quality of the previously reported analysis method can make a potential alternative for detecting glucose levels.

References

1. Villena Gonzales, W., Mobashsher, A., Abbosh, A.: The progress of glucose monitoring—a review of invasive to minimally and non-invasive techniques. Devices and Sensors. Sensors. **19**, 800 (2019). https://doi.org/10.3390/s19040800
2. Ogurtsova, K., da Rocha Fernandes, J.D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N.H., Cavan, D., Shaw, J.E., Makaroff, L.E.: IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res. Clin. Pract. **128**, 40–50 (2017). https://doi.org/10.1016/j.diabres.2017.03.024
3. Guariguata, L.: Contribute data to the 6th edition of the IDF diabetes atlas. Diabetes Res. Clin. Pract. **100**, 280–281 (2013). https://doi.org/10.1016/j.diabres.2013.02.006
4. Cho, N.H., Shaw, J.E., Karuranga, S., Huang, Y., da Rocha Fernandes, J.D., Ohlrogge, A.W., Malanda, B.: IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res. Clin. Pract. **138**, 271–281 (2018). https://doi.org/10.1016/j.diabres.2018.02.023
5. El-Safty, S.A., Shenashen, M.A.: Advanced nanoscale build-up sensors for daily life monitoring of diabetics. Adv. Mater. Interfaces. **7**, 2000153 (2020). https://doi.org/10.1002/admi.202000153
6. Pociot, F., Lernmark, Å.: Genetic risk factors for type 1 diabetes. Lancet **387**, 2331–2339 (2016). https://doi.org/10.1016/S0140-6736(16)30582-7
7. Patterson, C.C., Harjutsalo, V., Rosenbauer, J., Neu, A., Cinek, O., Skrivarhaug, T., Rami-Merhar, B., Soltesz, G., Svensson, J., Parslow, R.C., Castell, C., Schoenle, E.J., Bingley, P.J.,

Dahlquist, G., Jarosz-Chobot, P.K., Marčiulionytė, D., Roche, E.F., Rothe, U., Bratina, N., Ionescu-Tirgoviste, C., Weets, I., Kocova, M., Cherubini, V., Rojnic Putarek, N., deBeaufort, C.E., Samardzic, M., Green, A.: Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia **62**, 408–417 (2019). https://doi.org/10.1007/s00125-018-4763-3

8. Livingstone, S.J., Levin, D., Looker, H.C., Lindsay, R.S., Wild, S.H., Joss, N., Leese, G., Leslie, P., McCrimmon, R.J., Metcalfe, W., McKnight, J.A., Morris, A.D., Pearson, D.W.M., Petrie, J.R., Philip, S., Sattar, N.A., Traynor, J.P., Colhoun, H.M.: Estimated life expectancy in a scottish cohort with type 1 diabetes, 2008–2010. JAMA J. Am. Med. Assoc. **313**, 37–44 (2015). https://doi.org/10.1001/jama.2014.16425
9. Huo, L., Harding, J.L., Peeters, A., Shaw, J.E., Magliano, D.J.: Life expectancy of type 1 diabetic patients during 1997–2010: a national Australian registry-based cohort study. Diabetologia **59**, 1177–1185 (2016). https://doi.org/10.1007/s00125-015-3857-4
10. DiMeglio, L.A., Evans-Molina, C., Oram, R.A.: Type 1 diabetes. Lancet **391**, 2449–2462 (2018). https://doi.org/10.1016/S0140-6736(18)31320-5
11. Greenbaum, C.J., Speake, C., Krischer, J., Buckner, J., Gottlieb, P.A., Schatz, D.A., Herold, K.C., Atkinson, M.A.: Strength in numbers: opportunities for enhancing the development of effective treatments for type 1 diabetes—the trialnet experience. Diabetes **67**, 1216–1225 (2018). https://doi.org/10.2337/db18-0065
12. Weyer, C., Bogardus, C., Mott, D.M., Pratley, R.E.: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J. Clin. Invest. **104**, 787–794 (1999). https://doi.org/10.1172/JCI7231
13. Lyssenko, V., Almgren, P., Anevski, D., Perfekt, R., Lahti, K., Nissén, M., Isomaa, B., Forsen, B., Homström, N., Saloranta, C., Taskinen, M.R., Groop, L., Tuomi, T.: Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. Diabetes **54**, 166–174 (2005). https://doi.org/10.2337/diabetes.54.1.166
14. Cnop, M., Vidal, J., Hull, R.L., Utzschneider, K.M., Carr, D.B., Schraw, T., Scherer, P.E., Boyko, E.J., Fujimoto, W.Y., Kahn, S.E.: Progressive loss of β-cell function leads to worsening glucose tolerance in first-degree relatives of subjects with type 2 diabetes. Diabetes Care **30**, 677–682 (2007). https://doi.org/10.2337/dc06-1834
15. Sattar, N., Rawshani, A., Franzén, S., Rawshani, A., Svensson, A.M., Rosengren, A., Mcguire, D.K., Eliasson, B., Gudbjörnsdottir, S.: Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks: findings from the swedish national diabetes registry. Circulation **139**, 2228–2237 (2019). https://doi.org/10.1161/CIRCULATIONAHA.118.037885
16. The RISE Consortium: Lack of durable improvements in b -Cell function following withdrawal of pharmacological interventions in adults with impaired glucose tolerance or recently diagnosed Type 2 diabetes. Diabetes Care **42**, 1742–1751 (2019). https://doi.org/10.2337/dc19-0556/-/DC1
17. Tripathy, D., Schwenke, D.C., Banerji, M.A., Bray, G.A., Buchanan, T.A., Clement, S.C., Henry, R.R., Kitabchi, A.E., Mudaliar, S., Ratner, R.E., Stentz, F.B., Musi, N., Reaven, P.D., DeFronzo, R.A.: Diabetes incidence and glucose tolerance after termination of pioglitazone therapy: results from ACT NOW. J. Clin. Endocrinol. Metab. **101**, 2056–2062 (2016). https://doi.org/10.1210/jc.2015-4202
18. Eizirik, D.L., Pasquali, L., Cnop, M.: Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nat. Rev. Endocrinol. **16**, 349–362 (2020). https://doi.org/10.1038/s41574-020-0355-7
19. Thatikayala, D., Ponnamma, D., Sadasivuni, K.K., Cabibihan, J.J., Al-Ali, A.K., Malik, R.A., Min, B.: Progress of advanced nanomaterials in the non-enzymatic electrochemical sensing of glucose and H_2O_2. Biosensors **10**, 151 (2020). https://doi.org/10.3390/bios10110151
20. Chen, X., Wu, G., Cai, Z., Oyama, M., Chen, X.: Advances in enzyme-free electrochemical sensors for hydrogen peroxide, glucose, and uric acid. Microchim. Acta. **181**, 689–705 (2013). https://doi.org/10.1007/s00604-013-1098-0

21. Cheng, Z., Wang, E., Yang, X.: Capacitive detection of glucose using molecularly imprinted polymers. Biosens. Bioelectron. **16**, 179–185 (2001). https://doi.org/10.1016/S0956-5663(01)00137-3
22. Barone, P.W., Parker, R.S., Strano, M.S.: In vivo fluorescence detection of glucose using a single-walled carbon nanotube optical sensor: design, fluorophore properties, advantages, and disadvantages. Anal. Chem. **77**, 7556–7562 (2005). https://doi.org/10.1021/ac0511997
23. Alzahrani, E., Ahmed, R.A.: Synthesis of copper nanoparticles with various sizes and shapes: application as a superior non-enzymatic sensor and antibacterial agent. Int. J. Electrochem. Sci. **11**, 4712–4723 (2016). https://doi.org/10.20964/2016.06.83
24. Dayakar, T., Venkateswara Rao, K., Park, J., Sadasivuni, K.K., Ramachandra Rao, K., Jaya rambabu, N.: Non-enzymatic biosensing of glucose based on silver nanoparticles synthesized from Ocimum tenuiflorum leaf extract and silver nitrate. Mater. Chem. Phys. **216**, 502–507 (2018). https://doi.org/10.1016/j.matchemphys.2018.05.046
25. Wang, Q., Cui, X., Chen, J., Zheng, X., Liu, C., Xue, T., Wang, H., Jin, Z., Qiao, L., Zheng, W.: Well-dispersed palladium nanoparticles on graphene oxide as a non-enzymatic glucose sensor. RSC Adv. **2**, 6245–6249 (2012). https://doi.org/10.1039/c2ra20425h
26. Tian, K., Prestgard, M., Tiwari, A.: A review of recent advances in nonenzymatic glucose sensors. Mater. Sci. Eng. C. **41**, 100–118 (2014). https://doi.org/10.1016/j.msec.2014.04.013
27. Morris, N.A., Cardosi, M.F., Birch, B.J., Turner, A.P.F.: An electrochemical capillary fill device for the analysis of glucose incorporating glucose oxidase and ruthenium (III) hexamine as mediator. Electroanalysis **4**, 1–9 (1992). https://doi.org/10.1002/elan.1140040104
28. Yempally, S., Hegazy, S.M., Aly, A., Kannan, K., Sadasivuni, K.K.: Non-invasive diabetic sensor based on cellulose acetate/graphene nanocomposite. Macromol. Symp. **392**, 2000024 (2020). https://doi.org/10.1002/masy.202000024
29. Dayakar, T., Rao, K.V., Bikshalu, K., Malapati, V., Sadasivuni, K.K.: Non-enzymatic sensing of glucose using screen-printed electrode modified with novel synthesized CeO_2@CuO core shell nanostructure. Biosens. Bioelectron. **111**, 166–173 (2018). https://doi.org/10.1016/j.bios.2018.03.063
30. Ci, S., Huang, T., Wen, Z., Cui, S., Mao, S., Steeber, D.A., Chen, J.: Nickel oxide hollow microsphere for non-enzyme glucose detection. Biosens. Bioelectron. **54**, 251–257 (2014). https://doi.org/10.1016/j.bios.2013.11.006
31. Bayrakli, I., Erdogan, Y.K.: Photo-acoustic sensor based on an inexpensive piezoelectric film transducer and an amplitude-stabilized single-mode external cavity diode laser for in vitro measurements of glucose concentration. Opt. Laser Technol. **102**, 180–183 (2018). https://doi.org/10.1016/j.optlastec.2017.12.034
32. Vashist, S.K.: Non-invasive glucose monitoring technology in diabetes management: a review. Anal. Chim. Acta. **750**, 16–27 (2012). https://doi.org/10.1016/j.aca.2012.03.043
33. Kottmann, J., Rey, J., Sigrist, M.: Mid-Infrared photoacoustic detection of glucose in human skin: towards non-invasive diagnostics. Sensors. **16**, 1663 (2016). https://doi.org/10.3390/s16101663
34. Camou, S., Haga, T., Tajima, T., Tamechika, E.: Detection of aqueous glucose based on a cavity size- and optical-wavelength-independent continuous-wave photoacoustic technique. Anal. Chem. **84**, 4718–4724 (2012). https://doi.org/10.1021/ac203331w
35. Dumitras, D.C., Dutu, D.C., Matei, C., Magureanu, A.M., Petrus, M., Popa, C.: Laser photoacoustic spectroscopy: principles, instrumentation, and characterization. J. Optoelectron. Adv. Mater. **9**, (2007)
36. Rosencwaig, A.: Photoacoustic spectroscopy of biological systems. Science **181**(80-.), 657–658 (1973). https://doi.org/10.1111/j.1751-1097.1981.tb09074.x
37. Rosencwaig, A.: Photoacoustic spectroscopy, new tool for investigation of solids. Anal. Chem. **47**, 592–604 (1975)
38. Marín, E.: Escuchando la luz: breve historia y aplicaciones del efecto fotoacústico. Latin-American J. Phys. Educ. **2**, 17 (2008)
39. Lai, E.P.C., Chan, B.L., Hadjmohammadi, M.: Use and applications of photoacoustic spectroscopy. Appl. Spectrosc. Rev. **21**, 179–210 (1985). https://doi.org/10.1080/05704928508060430

40. Rosencwaig, A.: Photoacoustic spectroscopy of solids. Opt. Commun. **7**, 305–308 (1973). https://doi.org/10.1063/1.3069155
41. Hernández-Aguilar, C., Domínguez-Pacheco, A., Cruz-Orea, A., Ivanov, R.: Photoacoustic spectroscopy in the optical characterization of foodstuff: a review. J. Spectrosc. **2019**, 1–34 (2019). https://doi.org/10.1155/2019/5920948
42. Maugh, T.H.: Photoacoustic spectroscopy: new uses for an old technique. Science **188**(80-.), 38–39 (1975). https://doi.org/10.1126/science.188.4183.38
43. Zhilo, N.M., Rudenko, P.A., Zhigaylo, A.N.: Development of hardware-software test bench for optical non-invasive glucometer improvement. In: 2017 IEEE Conference of Russian Young Researchers in Electrical and Electronic Engineering (EIConRus). pp. 89–90. IEEE (2017)
44. Gusev, S.I., Simonova, A.A., Demchenko, P.S., Khodzitsky, M.K., Cherkasova, O.P.: Blood glucose concentration sensing using biological molecules relaxation times determination. In: 2017 IEEE International Symposium on Medical Measurements and Applications (MeMeA). pp. 458–463. IEEE (2017)
45. Sari, M.W., Luthfi, M.: Design and analysis of non-invasive blood glucose levels monitoring. In: 2016 International Seminar on Application for Technology of Information and Communication (ISemantic). pp. 134–137. IEEE (2016)
46. Lekha S., Suchetha M.: Non-invasive diabetes detection and classification using breath analysis. In: 2015 International Conference on Communications and Signal Processing (ICCSP). pp. 0955–0958. IEEE (2015)
47. Zhou, M., Wang, Z., Wang, X.: Carbon nanotubes for sensing applications. In: Industrial Applications of Carbon Nanotubes. pp. 129–150. Elsevier (2017)
48. Jia, J., Guan, W., Sim, M., Li, Y., Li, H.: Carbon nanotubes based glucose needle-type biosensor. Sensors. **8**, 1712–1718 (2008). https://doi.org/10.3390/s8031712
49. Aslan, K., Lakowicz, J.R., Geddes, C.D.: Plasmonic Glucose Sensing. In: Glucose Sensing. pp. 259–282. Springer US, Boston, MA (2007)
50. Lerner, M.B., Kybert, N., Mendoza, R., Villechenon, R., Bonilla Lopez, M.A., Charlie Johnson, A.T.: Scalable, non-invasive glucose sensor based on boronic acid functionalized carbon nanotube transistors. Appl. Phys. Lett. **102**, 183113 (2013). https://doi.org/10.1063/1.4804438
51. Ghazaryan, A., Ovsepian, S. V., Ntziachristos, V.: Extended near-infrared optoacoustic spectrometry for sensing physiological concentrations of glucose. Front. Endocrinol. (Lausanne). **9**, 112 (2018). https://doi.org/10.3389/fendo.2018.00112
52. Dasa, M.K., Markos, C., Janting, J., Bang, O.: Multispectral photoacoustic sensing for accurate glucose monitoring using a supercontinuum laser. J. Opt. Soc. Am. B. **36**, A61–A65 (2019). https://doi.org/10.1364/JOSAB.36.000A61
53. Christison, G.B., MacKenzie, H.A.: Laser photoacoustic determination of physiological glucose concentrations in human whole blood. Med. Biol. Eng. Comput. **31**, 284–290 (1993). https://doi.org/10.1007/BF02458048
54. Quan, K.M., Christison, G.B., MacKenzie, H.A., Hodgson, P.: Glucose determination by a pulsed photoacoustic technique: An experimental study using a gelatin-based tissue phantom. Phys. Med. Biol. **38**, 1911–1922 (1993). https://doi.org/10.1088/0031-9155/38/12/014
55. Wadamori, N., Shinohara, R., Ishihara, Y.: Photoacoustic depth profiling of a skin model for non-invasive glucose measurement. In: 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. pp. 5644–5647. IEEE (2008)
56. Ren, Z., Liu, G., Huang, Z.: Noninvasive detection of glucose level based on tunable pulsed laser induced photoacoustic technique. In: Czarske, J., Zhang, S., Sampson, D., Wang, W., Liao, Y. (eds.) International Symposium on Optoelectronic Technology and Application 2014: Laser and Optical Measurement Technology; and Fiber Optic Sensors, p. 929709 (2014)
57. Pai, P.P., Kumar Sanki, P., De, A., Banerjee, S.: NIR photoacoustic spectroscopy for non-invasive glucose measurement. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). pp. 7978–7981. IEEE (2015)
58. Sim, J.Y., Ahn, C.-G., Jeong, E.-J., Kim, B.K.: In vivo Microscopic photoacoustic spectroscopy for non-invasive glucose monitoring invulnerable to skin secretion products. Sci. Rep. **8**, 1059 (2018). https://doi.org/10.1038/s41598-018-19340-y

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