

Invasive and Non-Invasive Glucose Monitoring Systems: A Review and Comparative Study

Abstract. As the incidence of diabetes has expanded worldwide in recent years, an increasing number of patients are experiencing pain and infections because of the invasive nature of the majority of commercial glucose measurement systems. The availability of reliable, low-cost, painless, noninvasive technology will promote patient compliance to routine blood glucose monitoring. The life of the diabetic patient will thereafter significantly improve. Several technologies have been proposed and developed by scientists and researchers in an attempt to enhance their effectiveness. This study reviewed both invasive and non-invasive glucose monitoring techniques, with an emphasis on optical methods. Non-invasive glucose monitoring devices that are painless, sensitive, and transportable are being suggested and developed to better understand glucose levels.

Streszczenie. Ponieważ częstość występowania cukrzycy wzrosła na całym świecie w ostatnich latach, coraz większa liczba pacjentów doświadcza bólu i infekcji ze względu na inwazyjny charakter większości komercyjnych systemów pomiaru glukozy. Dostępność niezawodnej, niedrożej, bezbolesnej i nieinwazyjnej technologii ułatwi pacjentom przestrzeganie rutynowego monitorowania stężenia glukozy we krwi. Życie pacjenta z cukrzycą ulegnie następnie znacznej poprawie. Kilka technologii zostało zaproponowanych i opracowanych przez naukowców i badaczy w celu zwiększenia ich skuteczności. W badaniu tym dokonano przeglądu zarówno inwazyjnych, jak i nieinwazyjnych technik monitorowania glikemii, z naciskiem na metody optyczne. Sugerowane i opracowywane są nieinwazyjne urządzenia do monitorowania glukozy, które są bezbolesne, czule i przenośne, aby lepiej zrozumieć poziomy glukozy. (**Inwazyjne i nieinwazyjne systemy monitorowania glukozy: przegląd i badanie porównawcze**)

Keywords: Invasive, Non-invasive, Glucose, Optical.

Słowa kluczowe: pomiar glukozy, nieinwazyjny pomiar

Introduction

Most meals include complex carbohydrates, which give energy to cells. Sugars and glucose are produced during the digestion of carbohydrates in food. Glucose molecules are carried by the circulatory system from the gut to the liver and other organs [1]. As glucose levels in the blood rise, insulin is secreted by pancreatic beta cells. Post-meal glucose elimination is aided by insulin [2]. Diabetes mellitus is a long-term condition that interferes with metabolism. It is distinguished by unusually high blood glucose levels caused by either the pancreas failing to generate enough insulin due to autoimmune beta cell destruction (type one) or the body's cells reacting incorrectly to insulin due to a gradual loss in beta cell insulin production (type two) [3][4]. Diabetes is an opportune disease with a vast amount of information available and enormous problems[5].

To control blood sugar levels, the pancreas secretes the hormone insulin. Beta-cell failure is eventually caused by insulin resistance, poor management of hepatic glucose production, and diminishing beta-cell function in type 2 diabetes. Gestational diabetes mellitus is a condition that may manifest itself in a woman's body during the second or third trimester of pregnancy [6][7]. In order to prevent potentially fatal consequences like kidney failure, peripheral neuropathy, and cardiovascular illnesses, it is imperative to keep blood glucose levels within the normal range [8]. Having a glucose level below 60 mg/dL is referred to as hypoglycemia [9]. Contrarily, Hyperglycemia is described as having a glucose level more than 120 or 180 mg/dL whether fasting or eating [9][10]. (see Figure 1).

Diabetes is becoming more common everywhere. The World Diabetes Federation's most current projections show that the prevalence of diabetes among individuals aged 20 to 79 would be 10.5% (536.6 million) in 2021 and 12.2% (783.2 million) in 2045. The prevalence of diabetes was highest in those aged 75 to 79, and it was similar for men and women. In 2021, urban areas were expected to have a higher prevalence (12.1%) than rural areas (8.3%). The global cost of treating diabetes-related ailments was projected to reach \$966 billion in 2021 and to increase to

\$1,054 billion in 2045[11]. These numbers underscore the relevance of diabetes and drive scientists to discover innovative therapeutics to mitigate the disease's detrimental impacts.

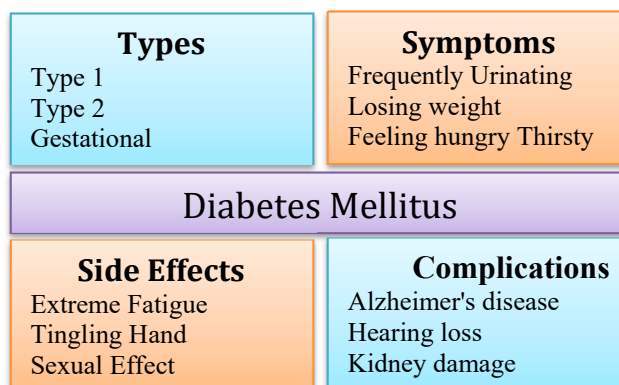


Fig1: Overview of Diabetes

The only way to improve patient with diabetes quality of life and keep them from developing serious consequences is through routine monitoring and control of blood glucose levels [12]. Various sensor kinds have been developed and studied. In 2010 a review study by Toghil and Compton offers a valuable perspective on the enzymatic and non-enzymatic electrochemical glucose detecting methods investigated during the previous decade [13]. Recently, a number of glucose monitoring methods have been created. Based on their mechanism, these technologies are divided into invasive and non-invasive categories [10][11][14]. Figure 2 depicts the majority of blood glucose measuring approaches.

Invasive Blood Glucose Monitoring Techniques

Non-invasive, minimally invasive, and invasive methods are used to detect blood glucose levels. According to the most up-to-date definition of an invasive technology, which is based on a review of medical journal articles, a glucose

monitor is considered an invasive glucose monitor (IGM) if it requires a lancing instrument to be used on the skin to collect blood samples [15]. Traditional methods, which are invasive, include laboratory methods and self-monitoring blood glucose (SMBG) devices, also known as glucometers [16]. Enzymatic-amperometric and hexokinase measurements are the two methods used in clinical labs to determine blood sugar levels [17]. Once patients have fasted overnight, their glucose levels are checked using an automated biochemical analyzer. This approach is not appropriate for continuous diabetes monitoring because of the lengthy process, detection time, and venous blood extraction required. Nonetheless, it might be utilised for identifying diabetic conditions.

Non-continuous glucose monitors (NCGMs) and continuous glucose monitors (CGMs) are the two categories of devices designed for use in self-testing and assessment at home. The frequency of using non-invasive continuous

glucose monitoring (NCGM) devices, also known as self-monitoring blood glucose (SMBG), to check blood sugar levels varies from person to person based on their clinical condition, type of diabetes, food, and medication dosage. [18]. In contrast, continuous glucose monitoring (CGM) devices may perform automated checks of blood glucose levels every few minutes, allowing for the identification of fast changes and patterns that would otherwise go unnoticed by SMBG testing. Nonetheless, both methods are suitable for use in self-assessment and point-of-care situations due to their accuracy and reliability [8]. Due to the simplicity of the measurement method and its reliance on capillary blood for precise glucose measurements make SMBG devices the gold standard in self-monitoring [18]. SMBG is the process of checking the blood glucose level at a particular moment in time [19]. SMBG should be taken four times daily, up to ten times daily during illness or poor control, according to medical standards [20].

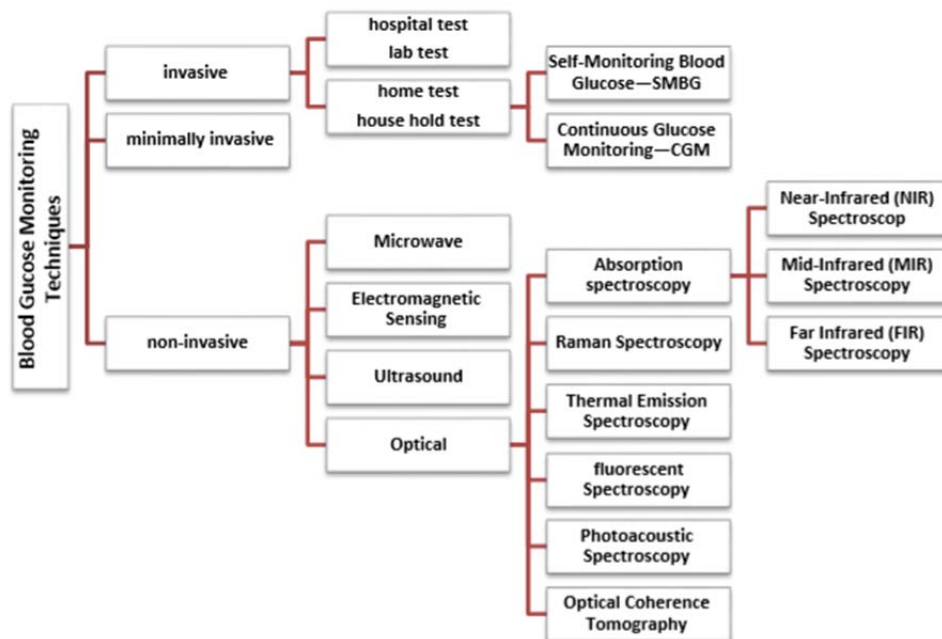


Fig 2. Measurement of Blood Glucose Classification Chart

Self-management tools allow people to measure their blood sugar levels over time and immediately before and after meals [21][22]. Finger-prick testing, an enzyme-based method of collecting blood from a fingertip and measuring it in vitro using test strips and a blood glucose metre (glucometer), is presently the most common method of self-monitoring [23][24][25]. Figure 3 depicts this. It is not a continuous way of monitoring blood sugar levels and must be repeated many times each day, especially before and after meals, physical exercise, and insulin delivery, to be helpful in treating high blood sugar see Figure 3 [12].

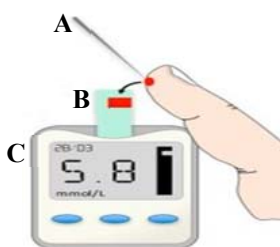


Fig 3: Finger-pricking tool. A lancet needle; B a blood sample on a test strip; and C a glucose meter showing the amount of glucose in mmol/L. Adapted from [12].

The three essential parts of a CGM device are a wireless receiver, a transmitter, and a sensor (implantable sensors). The sensor is a small detecting device implanted under the skin. The concentration of glucose in the blood is then calculated using an electrochemical technique [26]. CGM may also contain insulin infusion and management modules, such as an insulin pump [27][28]. Glucose monitoring is commonly performed using either subcutaneously implanted sensors or needle-based glucose metres [29] (see Figure 4).

Blood glucose levels in healthy individuals range from 4.9 to 6.9 mmol/L, but for individuals who have diabetes, they may climb to as high as 40 mmol/L after consuming glucose. When the blood glucose concentration drops below 3.9 mmol/L, a medical condition known as hypoglycemia occurs. Hypoglycemia has a larger risk coefficient among the elderly [30]. Regular monitoring of hypoglycemia at night may be difficult with the current methods of monitoring blood glucose levels. Because of this, strict regulation of blood glucose levels is associated with a higher probability of hypoglycemia. Continuous glucose monitoring (CGM), on the other hand, may have more therapeutic application value and be more in tune with the demands of diabetic customers generally [31].

These techniques have been used for about 50 years, and they have undergone constant development to demand less blood and take measurements more quickly [32]. Unfortunately, the expense, discomfort, blood waste, and calluses associated with this procedure make patients less enthusiastic about performing frequent glucose tests [32][33][34].

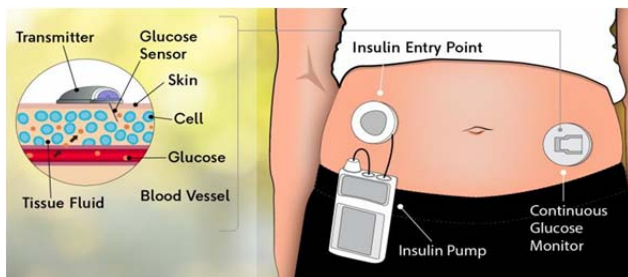


Figure 4. A CGM system consists of transmitter, glucose sensor, and receiver or display Adapted from [25]

Non-Invasive Blood Glucose Monitoring Techniques

Non-invasive (NI) blood glucose monitoring is the measurement of human blood glucose without causing any damage to human tissues. The purpose of NI blood glucose monitoring is to eliminate any discomfort or agony associated with obtaining a glucose measurement [35]. Non-invasive blood glucose monitoring is possible because the glucose molecule may participate in a wide variety of interior physical and chemical processes[36]. Throughout the last several years, the development of non-invasive blood monitoring methods has piqued the interest of both academics and medical equipment makers. If the glucose level recorded by the device varies greatly from the original glucose levels, the patient may be forced to take a high dose of insulin, which might be dangerous [37][38][39]. The precision of these devices is critical in calculating insulin dose. The non-invasive approach may be used to measure glucose at a variety of locations, including the skin, wrist, earlobe, fingertip, and others [34][26].

Non-invasive approaches for measuring blood sugar levels may be roughly classified as microwave [40], electromagnetic [41][42], ultrasound [43], and optical [44][14]. As shown in Figure 1, optical technologies [48][44] include near-infrared [45], far-infrared [46], mid-infrared [47], Raman spectroscopy [14], optical coherence tomography (OCT), and other optical methods. Glucose is found in a variety of bio-fluids, including saliva, tears, sweat, and ISF, in addition to large quantities in human blood [49][48][50][51][52].

These may be classified depending on the glucose sensing technology employed. The major sensing techniques for non-invasive technologies are electrochemical [53][31] and electromagnetic [14][42][54]. In electrochemical noninvasive glucose sensors, a salivary probe [55], tear drops [26], or exhaled breath [56] is evaluated. This is done so that they may be easily collected and accessible. Urine may also be used to assess glucose levels; however, this is not recommended for use with a CGM device [57][58]. As a result, saliva, tears, and exhaled air are advised [55]. These sensors are often known as biosensors [59]. Electromagnetic techniques are utilised based on how electromagnetic waves interact with the human body [52].

It's necessary to use post-processing to establish the relationship between the observed signal from multiple sensing modalities (in most cases, either current, voltage, or phase/frequency) and the blood glucose concentration.

The relationship between the recorded signal and the blood glucose level may be established using a simple proportionality formula (BGL). Yet, for reliable BGL extraction, a calibration method is necessary. The pervasive fear of data loss, however, necessitates the use of interpolation and extrapolation [60]. Noninvasive blood glucose monitoring technologies have various benefits. The following benefits are stated in the review: less costly, more cost-effective Without pain or suffering There is no need for any more needles. lowest possible health risk, Always double-check, Small size, Simple structure, heightened sensitivity More thorough and trustworthy information, Connectivity to the Internet of Medical Things (IoMT), There are wearable and non-wearable variants. Intelligent implantable medical devices Neural networks with biological interfaces, for example. Remote monitoring is a viable possibility.

Microwave Method

Microwaves are electromagnetic waves with wavelengths ranging from 1 mm to 1 m and frequencies ranging from 300 MHz to 300 GHz [42]. Microwave sensors are often used by scientists in the area of non-invasive blood glucose monitoring because to their great penetrability, absence of ionization, and mobility. They may swiftly penetrate biological tissues a millimeter or more thick, delivering advantages not available with traditional optical detection methods, especially in the low-frequency region. Microwaves, with their lower energy per photon and less air dispersion, may allow for deeper tissue penetration and more precise blood glucose readings [8].

Variations in blood glucose alter the dielectric constant [61] [8][62], which has a significant impact on microwave reflection, transmission, and absorption in tissues. Microwave diagnostics is based on the differentiation between the dielectric properties of healthy and sick tissues [31]. The rise and fall of human blood sugar levels cause only minor variations in dielectric properties, requiring the use of a very sensitive sensor. It is critical to apply the appropriate signal-processing technology in addition to having a multi-frequency resonator with high levels of accuracy and stability [8] [61][63-76].

Electromagnetic Method

Because of its various interactions, including as absorption, scattering, and transmission with specific molecules within the body, electromagnetic (EM) wave sensing has gotten a lot of attention [42][8]. With this approach, interaction of two inductors' magnetic fields is measured by current or voltage [68]. The dielectric properties of blood are measured using eddy current fluctuations as a signal. It entails sending a signal with a certain frequency to the main inductor and receiving a secondary inductor output. This approach does not involve ionisation of bodily components [34].

The tested medium is most responsive to variations in glucose concentration at an appropriate frequency. This technology operates between 2.4 and 2.9 GHz [69]; the device's effectiveness is dependent on the frequency used. The ratio of input to output voltages or currents has a negative correlation with glucose concentration. Also, the frequency of the signal is critical for sufficient coupling, however this is also impacted by sample temperature [70]. It is possible to isolate the influence of blood sugar levels and reduce the effects of potentially confounding components like cholesterol by focusing on a narrow frequency range. It's also quite harmless since it doesn't ionise the body's components [8].

Ultrasound

The time of ultrasonic wave propagation is used to determine the thickness of the material. The faster the glucose concentration, the quicker an ultrasonic wave travels through a medium, the farther it will go. The density of the medium and the strength of the intermolecular bonds within it determine the compressibility of the fluid or tissue, which in turn determines the acoustic velocity of low-frequency waves in the medium [71]. The linear acoustic impedance is affected by factors such as density and adiabatic compressibility, which in turn are affected by changes in the glucose concentration of the extracellular fluid [58]. The glucose levels indicated by an optical sensor are extracted using a low-frequency ultrasonic wave [34].

Optical Methods

The technique for developing noninvasive blood glucose detection that has received the most research is optical glucose sensing. There are many techniques that fall under the category of "optical technique," and all of these techniques may determine the amount of glucose in the skin without the use of samples by utilizing light, electric current, etc. [48]. Although cost-effective and comfortable for users, optical approaches are sensitive to environmental factors including temperature, pressure, skin moisture, humidity, and others [48]. For non-invasive blood glucose detections, a variety of optical techniques have been used. Table 1 lists each technique's benefits and drawbacks as well as its basic operating principle.

- **Absorption spectroscopy:** is a method for analysing the characteristics of being absorbed, reflected, and scattered by human tissue by passing near infrared (750 nm–2500 nm), mid-infrared (2500 nm–100,000 nm), or far-infrared light through it. The near infrared spectrum ranges from 750 nm–2500 nm, while the mid-infrared spectrum ranges from 2500 As a result of the interaction between light and tissue and blood, the irradiated light source is absorbed, reflected, and diffused [69] [72-75].
- **Raman spectroscopy:** is a method that takes use of the scattering of light. This is an important part of the method. The scattering phenomenon occurs as a consequence of molecular vibrations and oscillations, which are caused by

the shining of a monochromatic laser beam over the sample tissue. Some compounds, like glucose, have degrees of scattering that are wholly dependent on the concentrations of the molecules themselves [69][76-83].

- **Photoacoustic spectroscopy** By using photoacoustic spectroscopy, one may determine the magnitude of the acoustic pressure wave that is generated when laser light is shone on tissues. To create thermal energy from an aqueous glucose solution, an infrared laser is utilised to stimulate the solution, which then absorbs the light. As a direct result of the volumetric expansion that immediately follows, a photoacoustic pressure wave that is associated with glucose level is produced [84][85][8].
- **Thermal Emission Spectroscopy (TES):** employs infrared light emission rather than glucose absorption. The intensity of infrared emission is proportional to the quantity of glucose present in the target location of the body part [86][87][8].
- **Metabolic Heat Conformation:** This involves doing a multivariate mathematical analysis of blood flow rate, blood oxygen saturation level, and heat dissipation. The amount of heat created by glucose oxidation is proportional to the amount of dissipative oxygen and glucose in the body[88][89].
- **Ocular Spectroscopy:** This method places contact lenses made of hydrogel on the patient's eyes. The colour of the lens changes depending on the glucose levels in the blood. These colour changes are employed in order to determine the amount of blood glucose present in the tears of diabetics who are anxious [90][91].
- **Optical Coherence Tomography (OCT):** is a method that uses an ultraluminescent light source, a photo detector, an interferometer that is coupled to the reference arm, and the sample arm. When the incoming laser beam has been backscattered by the tissue complex, the difference in wavelengths of the reflected light from the sample arm and the reference arm may then be calculated. The delay connection is used as a basis for estimating blood glucose levels [69][92][93]

Table 1: The test areas, benefits, and limitations of optical blood glucose monitoring techniques.

Optical Technique	Test Area	Benefits	Limitations
Absorption spectroscopy	Earlobe, Palm, Forearm, Inner lip, Fingertip	More affordable. Possesses strong tissue penetration.	Low signal-to-noise ratio (SNR), Influenced by the makeup of the tissues.
Fluorescence spectroscopy	Eye, Finger, Upper arm, Abdomen.	Sensitive to an extreme degree and needing less calibration.	Depends on the thickness, color, and pigmentation of the skin. The tissue toxicity of the fluorophore dye is possible.
Raman spectroscopy	Wrist, Finger, Arm, Eye.	Less susceptible to changes in temperature, moisture, and light interference.	Unstable laser sources, low signal-to-noise ratios, and prolonged spectrum collection times.
Photoacoustic spectroscopy	Arm, Earlobe, Finger	Wider wavelength range of laser light from ultraviolet to near-infrared and better sensitivity.	Susceptible to external influences. susceptible to physiological chemicals' interferences.
Thermal Emission Spectroscopy (TES)		Less calibration is necessary. possesses high repeatability.	Not accurate. influenced by tissue thickness, motion, and temperature.
Metabolic Heat Conformation	Forearm, Earlobe, Fingertip	Less costly and feasible.	Interference from the surroundings.
Ocular Spectroscopy	Eye	Performed at the cornea of the eye, where light scattering is minimal.	Delay period between glucose levels and tear. The lens causes discomfort for diabetics.
Optical Coherence Tomography (OCT)	Eye, Forearm	Great resolution, strong penetration, and good SNR are its defining characteristics.	Responsive to movement and body temperature.
Optical polarimetry		Independent of changes in temperature and PH. Miniaturization is simple.	Sensitive to movement and the dispersion of tissues. Low glucose molecule specificity.

Optical polarimetry: is a method that measures the effect of optically active solute molecules, such glucose, on the rotation of incident light. This technique was developed in the 1960s. The polarisation of light, which is determined by the temperature, the amount of thickness, and concentration of dissolved substances, is used to quantify the levels of glucose in the blood. It was rubbed into the clear fluid that filled the eyelids [94].

Despite significant advancements and successes in invention of glucose monitors, a number of obstacles persist. Accuracy is a major barrier to the development of blood glucose monitoring technologies. [95][96][97]. Calibration of glucose metres on a regular basis is an additional difficult aspect. Before use, Most methods of noninvasively monitoring blood sugar include taking blood samples and undergoing elaborate calibration processes. Invasive capillary calibration of blood glucose monitors increases cost, pain, and tedious procedures [98].

A poor signal to noise ratio is an additional barrier to the development of noninvasive glucose sensors [99][100][101]. Poor linearity, sensitivity, and selectivity to glucose molecules in noninvasive glucose monitors diminish the signal intensity and precision of glucose measurement. Multisensing might improve the signal-to-noise ratio of glucose concentration estimation [102][103][104]. This model used a variety of non-invasive detection methods. The combination of multisensing with a proper estimation approach improves the accuracy of glucose prediction, according to a research. Artificial neural networks (ANN) are a model of self-calibration that enhances blood glucose monitor calibration [105][106]. As a result of extensive research and technical advancements, the ability to detect and monitor blood glucose levels is growing and becoming more practical. Current innovations in nanotechnology and the miniaturisation of biosensors have allowed the creation of glucose monitoring systems that are more accurate, comprehensive, and dependable.

Conclusion

The methods for determining the glucose levels in the blood must be portable, simple, accurate, low-cost, rapid, and energy-efficient. In addition to these benefits, patients will have a lot simpler time controlling their glucose levels if the therapy is pleasant and does not cause any discomfort. While constructing non-invasive models, it is important to take into account blood-altering illnesses, drugs, dehydration, and other conditions. In recent years, the field of medicine has collaborated with a wide variety of different fields, such as computer science, biology, physics, chemistry, and electrical engineering, to conduct extensive research on improving the reliability and durability of implanted sensors for invasive monitoring. This research has focused on finding ways to make the sensors more long-lasting. Methods of glucose monitoring that do not need invasive surgery and are being developed include those that are more sensitive, pleasant, and portable.

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