

The Progress Review on Non-Invasive Glucose Monitoring Techniques

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Abstract

More and more people are experiencing pain and infection as a result of commercial glucose meters because of the invasive nature of these devices, which is on the rise due to the global increase in diabetes. There has been a surge in interest in non-invasive blood glucose monitoring as a new treatment option for many people with diabetes. A review of recent developments in non-invasive blood glucose detection technology is presented in this paper, along with a discussion of the major challenges that have remained. Medical, materials, optics, electromagnetic waves, chemistry, biology, computational science, and other fields are covered by the technology. This paper discusses the benefits and limitations of non-invasive and invasive technologies. We can expect non-invasive blood glucose monitoring to become more efficient and cost-effective as wearable technology and transdermal biosensors continue to advance.

Keywords: Non-invasive, glucose biosensor, optics, microwave, electrochemistry, plasmon resonance; fluorescence; ultrasound.

1. Introduction

Chronic illnesses such as diabetes are quite frequent in humans. As a result of genetics, immunological illnesses, and other forces on the human body, the body's glucose levels become imbalanced, leading to hyperglycemia and a failure of glucose metabolism, among other symptoms.

Diabetes may be divided into two categories: type 1 and type 2. The majority of people with type 1 diabetes are children and adolescents, however, it can occur at any age. Type 1 diabetes is characterized by a lack of insulin production in the body, necessitating daily insulin injections to maintain blood glucose levels. Adults are more likely to develop type 2 diabetes, which accounts for around 90% of all diabetes cases. Type 2 diabetes is characterized by poor use of the insulin produced by the pancreas. People with type 2 diabetes typically require oral medicines or insulin to keep their blood glucose levels in check over time [2].

In the United States alone, WHO estimates that the number of people with diabetes will rise to 39.7 million by 2030 and 60.6 million by the year 2060, from an estimated 450 million people today to 700 million by that time [2].

The World Health Assembly will adopt a resolution in May 2021 calling for more emphasis on diabetes prevention and management. Access to insulin and other diabetes medicines and health products should be improved, regulatory requirements for these products should be harmonized to ensure they are all treated the same, and a web-based tool to share market transparency information should be evaluated for its feasibility and potential value [1].

Besides the health complications, diabetes has a major economic impact. According to the projections, the EU would spend 189.3 billion USD in 2021, the second highest average cost per person worldwide for diabetes. Consideration of appropriate self-management norms can reduce the health and financial strain. Regular physical activity has been shown to improve insulin sensitivity, glycaemic management, and psychological well-being in people with diabetes, and many different types of physical activity have been studied. When it comes to managing type 1 diabetes, there is a contradiction because most research shows that exercise does not enhance glycaemic control. Studies show that athletes with type 1 diabetes have poorer metabolic control than the general population, which exacerbates the disease. Continuous glucose monitoring (CGM) improves overall metabolic management for this group, allowing the individual to make clinical decisions about glycaemic excursions while exercising and thereafter. The ability to predict future exercise by anticipating additional carbohydrate consumption or effectively adjusting insulin dosages is an additional benefit of being aware of glucose level patterns before, during, and after exercise.

Additionally, there is a huge section of the population that is either undiagnosed or at high risk, despite the high number of people who have been diagnosed. Because of this, the diagnosis and treatment of diabetes has become a subject of enormous practical significance as well as economic benefits in many nations, particularly in industrialized countries.

Glucose is the primary source of cellular energy in the human body. Furthermore, glucose is found in intracellular fluids, interstitial fluids (ISF), tears, saliva, and urine in addition to blood glucose. Diagnosis of diabetes is now based mostly on blood glucose levels. Fasting blood glucose (FBG) for healthy persons should be 3.9–6.1 mM, and 2 hours after eating, it should be 7.8 mM or less, according to the WHO's 2009 recommendation. When blood glucose levels fall below 11.1 milligrams per deciliter (mg/dL), a diagnosis of diabetes can be made in patients with classic signs of the disease (polyuria, polydipsia, and unexplained weight loss). Hypoglycemia, on the other hand, can cause serious harm to the human body. As a side effect of insulin treatment or oral hypoglycemic medications, clinical hypoglycemia is defined as blood glucose concentrations below 3.9 mM that persist for longer than 5 minutes [3].

2. Methods for Monitoring Blood Glucose Concentration

Invasive testing, minimally invasive testing, and non-invasive testing are all types of blood glucose testing available

2.1 Invasive Blood Glucose Monitoring

Direct arterial entry was the first method used to detect blood glucose levels. Obtaining samples for testing using this approach is difficult and needs the assistance of a qualified medical expert.

For patients confined to a small space, such as in an ICU, the intrusive measuring approach is preferable since it minimizes patient pain. Diabetes patients in hospitals routinely get this treatment, which has been shown to be successful by a number of writers. An intrusive approach has the benefit of being extremely precise. Although this procedure is time-consuming, it is necessary to do a blood glucose level test at least 5-7 times a day.

2.2 Non-Invasive Blood Glucose Monitoring

Glucose levels in the blood without endangering human tissues. There are several non-invasive ways of detecting blood glucose, which may be grouped into the optical, microwave, and electrochemical categories.

2.2.1 Surface Plasmon Resonance

SPPs, the collective coherent charge-density waves induced by an electromagnetic field projected onto a thin coating of a highly conductive and chemically inert metal such as gold, are the basis for the concept of surface plasmon resonance. As a result, an electric field with exponential decay (evanescence) emerges, one that is extremely responsive to variations in the medium's refractive index (SPR resonance peak). Small changes in refractive index and a related shift in resonant frequency, known as a "SPR shift," are used to describe glucose level fluctuations in the sensing medium, leading to a shifted intensity-loss-dip in the SPR reflection intensity curve [4].

Advantages of Surface plasmon resonance

- Due to its traditional electrical model structure, it does not require statistical calibration models since it is highly sensitive to minor variations in blood glucose concentration

Disadvantages of Surface plasmon resonance

- Pays attention to movement.
- Calibration takes a long time and is quite sensitive to perspiration and temperature, making it bulky.

In recent years, SPR technology has advanced greatly, but the focus has been on clinical samples rather than non-invasive glucose detection because to the lack of sensitivity to tiny glucose concentrations. Thus, recent study aims to improve SPR's specificity by using various proteins with high glucose affinity on the surface of the metal layer. As a result, when glucose solution comes into contact with the sensor surface, the protein specifically absorbs glucose molecules, altering the refractive index of the interface in direct proportion to the quantity of glucose in the sample. If interstitial fluid can be reached, this approach can be used as a MI technique. Nanotechnology advancements have also led to the creation of a new generation of SPR sensors that can detect concentrations as low as pmol and amol, on the order of magnitude. [5].

2.2.2 Fluorescence

Using Stoke's shift, fluorescence technology is able to emit light at a certain wavelength after absorbing light from another source, resulting in the emission of light at a different wavelength. Analyte concentration may be determined using fluorophores, specialised molecules that produce fluorescent light with properties that are proportional to concentration [6]. Due to issues with low selectivity, irreversibility, interference, and analyte depletion when fluorophores directly bind glucose molecules, receptors, intermediary molecules, are required. They more efficiently bind glucose and can undergo reversible changes in their local properties, leading to altered fluorescence. Enzymes, boronic acids, glucose binding proteins (GBP), and even designed synthetic materials like as carbon nanotubes and quantum dots (QDs) may all be used to monitor a wide variety of spectrum characteristics, from UV to near-infrared, using various fluorescent approaches.[7].

Advantages of fluorescence technology

- Due to the high specificity of the molecule's optical characteristics, it is even possible to detect glucose concentrations as low as 25 μ M.
- The fluorescence intensity and decay durations can be used to determine the concentration of analyte.
- Not susceptible to light scattering

Disadvantages of fluorescence technology

- pH and oxygen levels might cause interference, making it vulnerable.
- The presence of foreign material in biological medium may provide a toxicity risk.
- It has a short fluorescence lifetime.
- Limitations due to deterioration in photostability and decreased capacity to recognise objects.
- There may be concerns with biocompatibility because of local tissue damage.
- Acquired the ability to autofluorize

2.2.3 Optical Polarimetry

The idea of "chiral molecules," i.e. molecules that can spin the plane of polarised light, is used in optical polarimetry. Because glucose is a chiral molecule, it has the ability to clockwise rotate the polarisation plane of a light beam. According to this equation, the laser beam's rotational frequency is proportional to its wavelength (typically between 780 and 400 nm), analyte concentration, optical path length, ambient temperature, and wavelength [8].

Advantages of Optical Polarimetry

- Optical components may be easily shrunk, allowing for great resolution.

Disadvantages of Optical Polarimetry

- Heat sensitivity, motion sensitivity, and, interference sensitivity from other optically active chemicals are all characteristics of this material.
- Up to 30 minutes of lag is possible.

2.2.4 Optical Coherence Tomography

Micrometer-resolution changes in the optical properties of bio tissues may be detected using OCT, an imaging technique based on the concepts of low coherence interferometry and coherent radiation. The technology, which was originally designed for ophthalmic tomographic imaging, has now been adapted to monitor glucose content in the skin.[9].

Advantages of Optical Coherence Tomography

- High signal-to-noise ratio, deep penetration, and resistance to changes in blood pressure, heart rate, or hematocrit are all advantages of this technology.

Disadvantages of Optical Coherence Tomography

- Tissue inhomogeneity is a concern for those who are particularly sensitive to variations in skin temperature and mobility.

2.2.5 Near-Infrared Spectroscopy

Because of the molecular vibrations and rotation of bonds inside molecules, near-infrared spectroscopy (NIRS) relies on absorption and scattering of wavelengths ranging from 780 nm to 2500 nm. Transmittance, reflectance (including diffuse reflectance), and interactance are the three primary measuring modalities. However, they all use a dispersive spectrometer as their basic technology.[10].

Advantages of NIR spectroscopy

- The signal strength is directly proportional to the concentration of the analyte, because water is transparent in the NIR band.
- Sample preparation is kept to a minimum.
- Glass or plastic containers, for example, have no effect on the method.

Disadvantages of NIR spectroscopy

- False readings can be caused by glucose distributions that are not uniform.
- For reliable glucose testing, the concentrations are too low.
- High scattering level and selectivity issues for glucose measurement.

2.2.6 Mid-Infrared Spectroscopy

MIRS, also known as fingerprint spectroscopy, is a vibrational spectroscopy method. That is why mid-infrared spectroscopy makes use of the same setup and absorption principles as NIR, but at frequencies ranging from 120 THz (2.5 μ m) to 30 THz (10 μ m), although others cite 12 THz (25 μ m) as the lower frequency limit. [11].

Advantages of NIR spectroscopy

- Glucose absorbs MIR radiation more strongly than NIR radiation, hence its concentration may be detected with greater precision thanks to the absorption of certain MIR wavelengths by glucose.

Disadvantages of NIR spectroscopy

- Only a few micrometres of penetration are possible.
- Because of the low penetration, only reflection is an option.
- Absorbs a lot of water.
- Expensive tools.

2.2.7 Raman Spectroscopy

Based on the Raman phenomenon, Raman scattering measures the amount of monochromatic light that is scattered. When a beam of light with a single wavelength strikes a surface, it scatters and travels in all directions. Elastic or Rayleigh scattering accounts for the vast majority of this radiation, whereas "inelastic scattering" or "Raman scattering" accounts for the remaining scattered radiation, which has a different wavelength. To put it another way, the rotational and vibrational states of molecular molecules are crucial to Raman spectroscopy, which can be used to detect specific absorption bands and quantify corresponding molecules. This means peak locations in the Raman spectrum show the vibrational modes of each functional group within that molecular structure. It is therefore clear that the Raman shift will be constant no matter what light wavelengths are being used. C-H stretching band, C-O stretching band, and C-C stretching band are the most prominent vibration modes in glucose [12].

Advantages of Raman spectroscopy

- Because it detects dispersed light, it may be used on any surface, including opaque ones, and it has a high degree of specificity.

Disadvantages of Raman spectroscopy

- Hemoglobin can interfere with the laser's wavelength and intensity, making it vulnerable to interference.
- It takes a long time to collect an item.

- The poor signal-to-noise ratio, fluorescence, and turbidity make it vulnerable to interference.

2.2.8 Far-Infrared Spectroscopy

Based on absorption of certain vibrations and rotations of weak bonds and heavy-atom bonds, Terahertz (THz) spectroscopy, or FIR spectroscopy, may be used to study materials in the range between 1000m and 30 THz (10 m). For non-invasive glucose measurement, the lack of information of FIR implies that the technology is still in its infancy since the intense absorption of water and the low amounts of power given by terahertz sources do not allow useful data to be gathered using normal NIR and MIR procedures. It is now feasible to apply submillimeter-wavelength biomedical applications of time-resolved far-infrared spectroscopy (also known as Terahertz time-domain spectroscopy THz-TDS) thanks to quantum-cascade lasers (QCLs).[13].

Advantages of FIR spectroscopy

- Infrared has a lower scattering coefficient than infrared and mid-infrared

Disadvantages of FIR spectroscopy

- The detection of additional molecules in the sample is complicated by the sample's high water absorption.

2.2.9 Time of Flight (TOF) and Terahertz Time-Domain Spectroscopy

It employs picosecond laser pulses to measure the time it takes photons to move over a sample, and the radiation absorption is measured using a single-frequency laser pulse. Absorption and scattering are still used, but from a time-domain perspective to gain an extra parameter, phase change. There will be some photons that travel straight to the detector, while others may take a longer zigzagging course due to many internal reflections, while yet others may experience complete scattering and therefore produce diffuse light when traveling through the sample. The optical characteristics of the medium, including glucose content, may be measured by analyzing the time of flight distribution of received photons, changes in pulse shape (pulse broadening owing to scattering), and the absorption level. Because it employs ultrashort pulses in the time domain (a few hundred femtoseconds) for phase information measurement, THz-TDS is very similar to TOF, which uses ultrashort pulses (a few hundred femtoseconds). When compared to other methods, THz-TDS has the advantage of allowing for a much wider range of frequencies to be measured since it employs an ultrafast laser pump with a specified pulse shape (such as Gaussian or differentiated Gaussian). As a result, the detected signal may be analyzed spectroscopically, and the refractive index and spectrum of the complicated permittivity can be measured across a wide frequency range in a single scan. It is also feasible to extract frequency-dependent information such as dynamic range, bandwidth, and the signal-to-noise ratio utilizing specialized time-domain processing techniques.[14].

Advantages of TOF and THz-TDS

- A single ultrashort pulse can be used to study a wide variety of frequencies.

- Measurement of complex permittivity in just one scan

Disadvantages of TOF and THz-TDS

- Insufficient spatial and depth resolution Long measuring time.

2.2.10 Thermal Emission Spectroscopy (TES)

Far-infrared radiation (with wavelengths ranging from 8 μm to 14 μm) emitted by the human body is the basis for the TES method. Because glucose, which has a wavelength of 9.4 μm , absorbs some of this radiation as it leaves the body, measurements of the intensity and characteristics of this radiation can provide useful information on the presence and concentration levels of glucose in tissue with a reasonable degree of granularity and accuracy. However, due to the modest quantities of thermal energy involved, just monitoring and interpreting the radiation absorbed by glucose is insufficient to produce reliable measurements. As a result, TES uses the Planck distribution function to compare the recorded data with a projected quantity of thermal energy, which is used to determine the actual thermal absorption and then convert it to glucose concentration.[15].

Advantages of thermal emission spectroscopy

- Because of the well-defined spectra of glucose at 9.4 μm and the lack of need for calibration, this is a passive approach with no danger of tissue damage.

Disadvantages of thermal emission spectroscopy

- The radiation intensity is dependent on the tissue's thickness, hence it may not be suited for detecting abrupt changes in glucose levels.

2.2.11 Metabolic Heat Conformation (MHC)

Based on the creation of metabolic heat and local oxygen supply, MHC technology measures glucose levels by analyzing these physiological characteristics. An important part of the approach is the fact that glucose metabolism creates a specific amount of heat as a by-product that correlates with the amount of glucose and oxygen in the body. This heat corresponds to glucose and oxygen levels. Radiation, convection, and evaporation are all ways in which heat is dissipated into the atmosphere. Convection and radiation are connected to skin and ambient temperatures, whereas evaporation is the quantity of evaporation from the skin that is dissipated.[16].

Advantages of MHC

- Using well-established technology, it is quite simple to monitor physiological markers.

Disadvantages of MHC

- Environmental factors, such as temperature, might affect one's performance, making one more likely to overheat.

2.2.12 Photoacoustic Spectroscopy

Short laser pulses with a wavelength absorbed by a particular molecule in the fluid are used to induce tiny localised heating, which is reliant on the tissue's specific heat capacity. This technique is based on the same principle as ultrasonic waves. An acoustic or pressure sensor may detect an ultrasonic wave generated by the expansion of the medium as a result of the absorbed heat. It is feasible to link fluctuations in blood glucose levels to the peak-to-peak changes in the observed signal [17].

Advantages of photoacoustic spectroscopy

- Not sensitive to NaCl, cholesterol, or albumin, the PA signal is not affected by scattering particles. Relatively easy procedure.

Disadvantages of photoacoustic spectroscopy

- Temperature, pulsation, motion, and ambient acoustic disturbance all have an effect on the sensitivity of the sensor.
- It takes a long time to become used to the system.

2.2.13 Millimeter and Microwave Sensing

It is possible to get more precise glucose readings from millimeter and microwave radiation because they have lower energy per photon and less dispersion in the tissue, which enables them to penetrate deeper into the tissue and reach areas with appropriate blood concentration. Millimeter and microwave methods, which are extensively employed in a variety of fields, including communications, detection, and medicine, use tissue and blood's permittivity and conductivity in those bands to correlate glucose content in the body. Reflexion methods are one-port approaches that focus on detecting reflection parameters in an effort to determine the amplitude and phase fluctuation in the signal owing to the change in blood glucose permittivity. Because transmission techniques include the whole S-parameter set, they can calculate the complex propagation constant of the medium and hence the transmitted signal's attenuation or phase insertion as a result of changes in glucose concentration. Because it utilises a near-field sensor with a very high quality-factor Q , the resonant perturbation technique is a subset of reflection and transmission methods. Resonant frequency, quality factor, and 3dB bandwidth changes are to be correlated with changes in dielectric characteristics of the material under evaluation.[18].

Advantages of millimeter and microwave sensing

- There is no risk of ionisation since the signal penetrates deeply enough to reach tissues with adequate glucose.

Disadvantages of millimeter and microwave sensing

- Sensitive to fluctuations in physiological characteristics such as breathing, sweating, and heart rate;

- Susceptible to biological variances in blood;
- Poor selectivity.

2.2.14 Electromagnetic Sensing

The magnetic coupling between two inductors is proportional to the current or voltage measured by this technique. Coupling is proportional to analyte concentration and type since it is dependent on the dielectric properties of the medium between the two coils. the level of glucose in the blood. To provide sufficient coupling, both the frequency of the signal and the temperature of the sample must be taken into consideration. As a result, it is generally acknowledged that frequencies between 2.4 MHz and 2.9 MHz are acceptable for detecting glucose changes in vivo [19].

Advantages of electromagnetic sensing technology

- There is no chance of ionization since the analyte has a fixed frequency. There is no interference from other media.

Disadvantages of electromagnetic sensing technology

- Highly sensitive to temperature.

2.2.15 Bioimpedance Spectroscopy

Known as dielectric impedance spectroscopy, this technique examines changes in the membrane permittivity and conductivity of red blood cells as a result of changes in blood glucose (RBCs). The conductivity of the RBC membrane is thought to be directly related to the concentration of glucose in the plasma, according to BS, which assumes that changes in glucose concentration cause changes in sodium and potassium ion concentrations. This is done by measuring resistance and conductivity by applying a tiny quantity of alternating current with a specified intensity. This indicates that the process is simple, making it potentially economical and simple to use in a real environment, provided that sensitivity to temperature fluctuations and sweat, among other constraints, are taken into consideration.[20].

Advantages of bioimpedance spectroscopy

- Cost-effectiveness and ease of skin measuring are the primary advantages of this technology.

Disadvantages of bioimpedance spectroscopy

- Highly responsive to changes in environmental conditions, including changes in temperature and movement.
- Influenced by physiological factors that impact the cell membrane, such as sweating and dehydration.

2.2.16 Ultrasound

Ultrasound waves' propagation across medium can be measured using this method. Ultrasonic waves travel quicker through medium with increased glucose concentrations, resulting in shorter propagation times. The acoustic velocity of low-frequency waves in a medium is determined by the compressibility of the medium and the strength of the intermolecular bonding interactions.[21].

Advantages of Ultrasound technology

- Ultrasound technology's advantages include its ability to penetrate deep into tissue and its insensitivity to changes non-skin colour.

Disadvantages of Ultrasound technology

- Ultrasound technology has certain drawbacks, such as the fact that it is vulnerable to changes in temperature.

3. Glucose Monitoring Informatics (GMI)

In order to improve sensor accuracy and reliability, readability of data, and compensation for disturbances from various environmental and physiological processes, such as blood perfusion, tissue scattering, sweating, and temperature changes, different algorithms are being developed in tandem with the development of more sensitive sensors using various technologies [22]. Closed-loop devices for insulin pumping in diabetic patients can also benefit from these algorithms. Algorithms may be broken down into two categories: Algorithms aimed at reducing systematic discrepancies and distortions in the signal itself are the first step in corrective algorithms that are designed to improve signal quality. The so-called predictive algorithms fall into the second category, and they use a variety of different data sets to anticipate future glucose levels or improve on the one being measured right now.

4. Conclusion

It has been possible to gain a technical understanding of the current methods and equipment available for the non-invasive measurement of blood glucose levels in this study. Techniques and methods to evaluate their correctness, as well as standard equipment and devices, as well as the electromagnetic spectrum in which most research is taking place, have been described in depth. This part has been included to highlight how the existing characteristics of glucose detection reflect future technological progress and development of devices that can monitor glucose concentrations non-invasively.

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