# Non-Invasive Glucose Monitoring: A Review on Glucose Monitoring Devices and Technologies

Bhushan Potdar[1*], Kiran Pimpale[2], Sahil Agrawal[3], Jaib Shaikh[4], Laxmiprasad Khochage[5], Nilesh Chougule[6]
Students[1-4], Ashokrao Mane Institue of Pharmacy, Ambap.
Assistant Professor[5], Ashokrao Mane Institue of Pharmacy, Ambap.
Principal[6], Ashokrao Mane Institue of Pharmacy, Ambap.

**Abstract: Diabetes mellitus is a global health concern, necessitating frequent monitoring of blood glucose levels to manage the condition effectively. Non-invasive glucose monitoring technologies have garnered significant attention due to their potential to reduce the discomfort and inconvenience associated with traditional blood-based methods. This review provides a comprehensive overview of non-invasive glucose monitoring devices, the technologies employed, and the promising methods for glucose detection in bodily fluids such as saliva, sweat, and tears. The review begins by discussing the limitations of invasive glucose monitoring, emphasizing the need for non-invasive alternatives. It then explores various non-invasive glucose monitoring devices currently available, categorizing them into optical, electrochemical, thermal, and other emerging sensor technologies. Each category is examined in detail, highlighting their principles of operation and key advantages and limitations. A significant portion of this review is dedicated to the emerging field of glucose detection in bodily fluids beyond blood. Saliva, sweat, and tears offer potential alternatives for non-invasive glucose measurement. The technologies utilized for glucose detection in these bodily fluids, such as spectroscopy, microfluidics, and biosensors, are thoroughly discussed. The review also considers the factors affecting the accuracy and reliability of non-invasive glucose measurements, including physiological and environmental variables. Methods of glucose monitoring makes bright future for detection of blood glucose level and minimise efforts for controlling diabetes.**

**Key words: Diabetes, Non-invasive glucose monitoring, Glucose monitoring devices, non-invasive glucose monitoring technologies.**

## INTRODUCTION:

One of the most prevalent chronic diseases in humans that last a lifetime is diabetes. The primary causes of it include genetics, immunological illnesses, and other conditions affecting the human body that result in insulin resistance, a loss in islet function, and an imbalance in the body's glucose levels, which manifest as hyperglycaemia and failure of glucose metabolism [1]. Type 1 and type 2 diabetes are the two subtypes of the disease. Diabetes type 1 is brought on by insufficient insulin production by the pancreas. Conversely, type 2 diabetes is mostly brought on by patients inefficient use of insulin as a result of declining insulin sensitivity and insulin resistance [2].In every nation, diabetes mellitus (DM) is a leading cause of death and morbidity. Globally, around 366 million individuals suffered with diabetes in 2011. By 2030, it is predicted that 552 million people worldwide will have diabetes mellitus (DM), a result of the world's aging populations, increasingly poor diets, sedentary lifestyles, and obesity [3]. Type 1 diabetes is an autoimmune disease with pancreatic islet beta cell destruction. The condition is autoimmune, meaning that the body is unable to manufacture enough insulin. The most common type of diabetes, type 2, is caused by insulin resistance combined with an insulin secretory abnormality. Diabetes Types 1 and 2 are chronic illnesses that are typically difficult to treat [4]

Methods of Glucose Monitoring:

a. Invasive Methods of Glucose Monitoring

At present, invasive blood glucose detection technology is mainstream, convenient and practical, so both hospitals and household glucometers adopt the method of blood sampling first and then analysing it in vitro for blood glucose measurement. In medical facilities, blood is extracted from patients in the morning when they are fasting, and an automated biochemical analyzer precisely determines the blood glucose level. This method's high amount of venous blood extraction, long detection time, and laborious technique make it unsuitable for continuous monitoring of diabetics, even though the results are accurate and can serve as a valuable foundation for diabetes diagnosis [5].

Self-monitoring of blood glucose (SMBG) is the process of tracking blood glucose levels at a given moment using an electronic glucose meter that is often kept at home. On the other hand, most home blood glucose monitors employ glucose oxidase biosensors, draw blood from the fingertip using a disposable paper strip, and use the strip's chemical reaction current to calculate the blood glucose concentration. The most popular brands of commercial glucose meters available right now include Roche, Sano, Omron, Johnson & Johnson, Bayer, Abbott, Echeng, Ecco, and so on.

Advantages:

portability, affordability, ease of use, reasonably accurate data, and frequent monitoring throughout the day.

Disadvantages:

Before every test, a specific volume of blood is drawn from the fingertips; this causes deep skin punctures; the frequency of blood collection increases; and patients' fingertip wounds take longer to heal [5,6].

b. Non-Invasive Blood Glucose Monitoring

As the name suggests, non-invasive blood glucose monitoring is the process of measuring blood glucose levels in humans without harming their cells. Non-invasive blood glucose detection techniques are numerous and can be broadly categorized into three categories: optical, microwave, and electrochemical. Optical techniques include fluorescence, optical coherence tomography (OCT), polarized optical rotation, Raman spectroscopy, near-infrared reflectance spectroscopy (NIRS), and more [7,8].

GLUCOSE MONITORING DEVICES

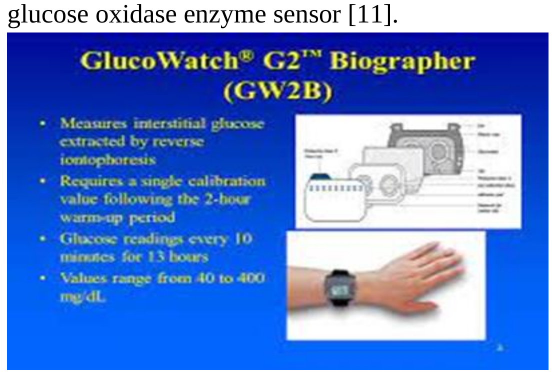
A promising area of diabetes research, glucose monitoring devices have the potential to benefit more than 400 million individuals globally. It is anticipated that this figure will increase by almost 55% during the next 25 years [9]. The need for an affordable, small, painless, and non-invasive gadget that can reduce the discomfort of frequent skin pricking and encourage regular glucose testing, which aids in blood glucose control, has grown over the past few decades [10].

Devices used in Glucose Monitoring:

1. GlucoWatch:

GlucoWatch G2 Biographer Cygnus Inc, USA was the first commercial device that was registered as a non-invasive glucose monitoring device and is the only product known as 'non-invasive' that was approved by the Food and Drug Administration FDA. However, the method used by the device—which is regarded as minimally invasive—was the extraction of interstitial fluid via the skin. The item was included in this study because it was registered as non-invasive. GlucoWatch is a significant contributor to the advancement of non-invasive technology and, as such, should not be overlooked.

The wristwatch-style gadget known as GlucoWatch was used to test interstitial glucose concentrations in real time at intervals of ten minutes. Adults and children with type 1 or type 2 diabetes were to utilize the device. The apparatus employed reverse iontophoresis to quantify the quantity of glucose molecules gathered via a cathode disk equipped with a glucose oxidase enzyme sensor [11].




img: Glucowatch G2 Biographer [12]

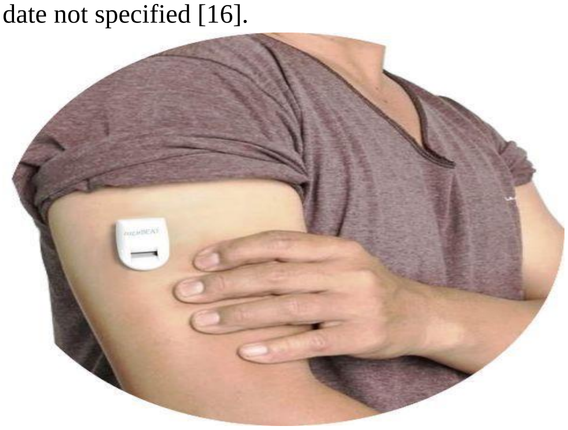
2. Pendra:

Pendragon Medical Switzerland unveiled Pendra, a continuous non-invasive wristwatch that used impedance spectroscopy, about 20 years ago. Sweating and motion caused problems, and the gadget needed to be calibrated. The gadget was taken off the market after a post-marketing validation study found that the accuracy was low, with 4.3% of readings out of 139 matched values in error zone E of the Clarke error grid CEG and a mean absolute relative difference of 52% [13]. However, Biovotion AG, Zurich, Switzerland, presently owns the intellectual property portfolio for this gadget and is working on a multisensory idea for ongoing non-invasive health parameter monitoring [14].


img. 2: Pendra- a glucose monitoring device [15]

3. SugarBEAT:

SugaeBeat is a non-invasive patch with an electronic sensor that uses interstitial fluid extracted from the skin to detect readings in real time. The patch is roughly 1 mm thick and disposable. Every reading is sent to an app that SugarBeat is connected to. Release date not specified [16].



img. 3: Needle-free Diabetic Device: Sugarbeat [17]

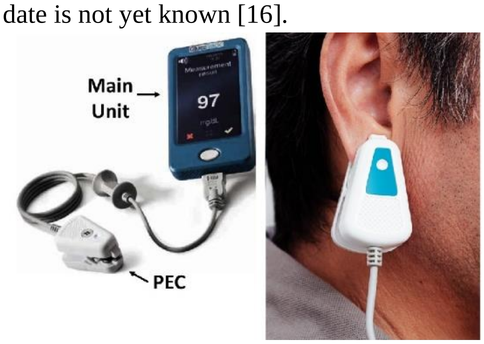
4. C8 Medisensors:

Raman spectroscopy was used by the C8 MediSensors Optical Glucose Monitoring System CA, USA. This method measures the vibrations of glucose molecules in response to a light beam shining into the skin. Every five minutes, this device continuously measured glucose. The fact that it doesn't require calibration against blood glucose readings is one of its primary benefits. Mean absolute differences were 38 mg/dL N=30, with the percentage of points in the A zone and the A+B CEG zones being 53% and 92%, respectively [18].


img. 4: C8 medisensor Device [19]

5. GlucoTrack:

Clips to the patient's earlobe in order to test the blood sugar level. The ear clip, which actually takes the measurements, and the main unit (MU) make up the gadget. It simultaneously makes use of three separate technologies: thermal, electromagnetic, and ultrasonic. The user's glucose level is determined via a proprietary algorithm that combines these data and computes a weighted average. Clinical studies are anticipated to start in the US in early 2017; a release date is not yet known [16].




img. 5: Performance and user experience evaluation of device GlucoTrack [20]

Challenges Occurs While Using Glucose Monitoring Devices:

The indirect nature of the measurement and the necessary calibration process are the main challenges in the development of non-invasive glucose sensors. This could lead to decreased accuracy, poor usability, and decreased applicability for household use, all of which would need significant work to overcome. Finding practical answers to these obstacles will mark a substantial advancement in this area [21].

1. Accuracy (device calibration):

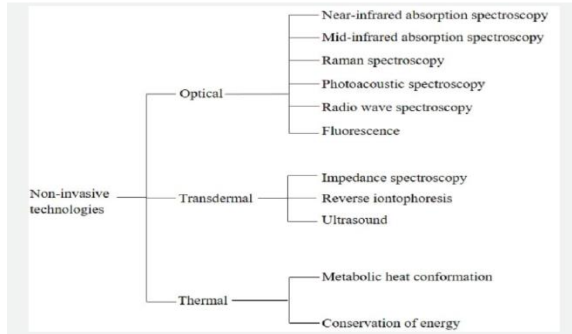
Since non-invasive measurements are indirect, they must be calibrated against current blood glucose data in order to estimate the concentration of glucose. To reduce the influence of individual quasi-stable parameters, such as tissue thickness and structure, the instrument is calibrated before usage. Depending on the instrument and technology used, this procedure usually entails multiple paired invasive-non-invasive measurements at varied frequencies. Given that calibration is thought to be the source of discomfort [22]. The majority of non-invasive gadgets need a drawn-out, intricate calibration procedure. For instance, the OrSense NBM-200G needed four measurements every hour for a three-hour calibration period every day [23]. Another is Pendra, which needed a two- to three-day patient-tailored calibration process [24].

2. Suitability for various people:
For non-invasive devices to achieve optimal performance, they must be appropriate for a wide range of consumers. This is difficult since the majority of the technologies that are used to estimate glucose indirectly are affected by human factors that interfere, like skin features [25].

3. Physiological time lag:
The accuracy of indirect glucose monitoring is reduced by the physiological temporal lag between blood and tissue glucose levels. This has historically been a significant problem for CGMs. It was demonstrated that the time lag varied depending on the measurement place and the individual's characteristics. This problem may also affect devices like GlucoTrack that measure glucose from the entire skin. The characteristics of the epidermis layer, such as the amounts of interstitial fluid, cells, and blood, affect the lag time of glucose dynamics [26,27].

## NON-INVASIVE GLUCOSE MONITORING TECHNOLOGIES

Many potential methods of non-invasive blood glucose monitoring have been studied. They consist of computer and microsensor technologies, as well as optical, chemical, and electrical methods [28]. Continuous glucose monitoring measures the amount of glucose in the interstitial or tissue fluid (ISF) using minimally invasive procedures [29]. Optical methods use the various characteristics of light to interact concentration-dependently with glucose. With transdermal approaches, ultrasonography or electricity are used to monitor glucose via the skin. Last but not least, thermal methods seek to quantify glucose by identifying physiological markers linked to the production of heat during metabolism [30,31].



img. 6: Non-Invasive glucose monitoring technologies [32]

1. Near-infrared Absorption spectroscopy:
The only non-invasive blood glucose monitoring device that has ever been approved for marketing by a public Food and Drug Administration (FDA) panel is NIR spectroscopy. Even though authorization was denied, the 1996 hearing was covered by the media [33]. When an external light source is used, the term "near-infrared light" describes light with infrared wavelengths that are close to visible light wavelengths. A bodily part may reflect or pass through an NIR source. The body's components, including glucose, absorb a tiny portion of light at each wavelength [34]. The wavelength range that is used for near-infrared (NIR) spectroscopy is 730–2500 nm. The idea is comparable to MIR spectroscopy. Broad bands that represent overlapping peaks make up the first, second, third, and combination overtones in NIR spectra, which are created by molecular vibrations. It enables the assessment of blood glucose in tissues through changes in light intensity, which are dependent on transmittance and reflectance. One of the forerunners in non-invasive blood glucose monitoring, Heise et al., has written extensively on NIR methods [35-37]. Usually, the fingers, earlobes, forearms, lips, oral mucosa, etc. are chosen as the NIR measuring sites. However, tests taken on the inside of the lips, where blood glucose levels and optical density are associated, yield better results than those taken on the fingers [38,39].

Advantages:
a. The primary benefit of NIR spectroscopy is the great sensitivity of the photoconductive detectors.

b. Water can be utilized for blood glucose monitoring since it is quite transparent to the NIR signal spectrum.

Limitations:
a. Researchers are still unable to overcome significant obstacles despite a great deal of promising work. These include the need for scanning pressure, physiological variations unrelated to blood glucose, the relatively small amount of glucose in blood, weak correlation, hardware sensitivity and stability, and physiological differences.

2. Mid-infrared Spectroscopy:
Using the same concepts as infrared spectroscopy, mid-infrared (MIR) spectroscopy measures MIR frequency by absorption by a sample placed in the beam's path. It is based on light with a wavelength between 2500 and 25,000 nm. Certain modeling tools in spectrum quantitative analysis can describe absorption discrepancies when MIR light encounters human tissues [40].

Advantages:
a. When comparing MIR spectroscopy to near infrared (NIR) spectroscopy, the higher wavelengths in MIR result in less scattering phenomena but more absorption [40].
b. Skin can be penetrated by light down to a few micrometres. Because no light is transmitted through a body segment, only reflected light may be taken into account.

Limitations:
a. Poor penetration is MIR's primary drawback. Similar to NIR, additional restrictions include issues with confounding variables such blood water content [41].

3. Raman Spectroscopy:
Using a visible to mid-infrared laser radiation source, Raman spectroscopy detects the scattered light in transparent samples, which has a greater wavelength and a lower intensity than the original light [42]. Besides reducing the spectral acquisition time, surface-enhanced Raman spectroscopy may also improve the sensitivity of glucose detection. However, before it is used on humans, the photothermal harm to eyes needs to be thoroughly studied [43].

The foundation of Raman spectroscopy involves rotating and oscillating human fluids that contain glucose using a laser. Because molecular vibration affects scattered light emission, the concentration of glucose in human fluids can be estimated [44].

Advantages:
a. When compared to NIR spectroscopy, Raman spectroscopy typically yields spectra that are crisper and less overlapped.

Limitations:
a. The primary constraints are associated with extended spectrum acquisition durations and laser wavelength and intensity instability.

4. Photoacoustic Spectroscopy:
It is predicated on how a projected laser beam interacts with tissue cells, producing heat and pressure changes in the sample that result in acoustic waves that may be detected by a piezoelectric transducer [45]. Specific incident laser beam wavelengths can be used to selectively detect blood glucose [46].

Advantages:
a. Water has little effect on the technique because of its low photoacoustic sensitivity.

Limitations:
a. Temperature sensitive.
b. Sensitive to pressure and other environmental factors.

5. Fluorescence:
This method tracks the presence of glucose molecules in blood using fluorescent reagents. There are numerous methods, such as monitoring changes in the energy transfer between a fluorescent donor and an acceptor during fluorescence resonance or quantifying the changes in enzyme intrinsic fluorescence brought on by glucose [47]. This method uses ultraviolet light at precise frequencies to excite tissues, and then it looks for fluorescence at a specified wavelength. Using polymerized crystalline colloidal arrays that react to varying glucose concentrations by diffraction of visible light, glucose in tears has been detected fluorescence-based [48].

Advantages:

a. This is a very sensitive device that can identify individual molecules.
b. It does not cause harm to the body.

Limitations:
a. Strong scattering phenomena can be problematic for photonic sensing, particularly in fluorescence technologies [49].

6. Bioimpedance Spectroscopy:
Its foundation is the use of known- intensity alternating currents to evaluate the impedance of a tissue. Measurements of the impedance (dielectric) spectrum are made in the frequency range of 100 Hz to 100 MHz at various wavelengths. By altering the quantities of $Na+$ and $K+$ ions, variations in the glucose concentration of plasma affect the membrane potential of red blood cells (RBCs) [50]. The impedance spectrum then indicates the variations in the membrane potential of RBCs [51,52].

Advantages:
a. It is not necessary to employ statistically- derived, population-specific prediction models when using bioimpedance spectroscopy.
b. It may have the benefit of describing the blood's bioimpedance characteristics by distinguishing between extracellular and intracellular water and, consequently, estimating body cell mass.

Limitations:
a. This technology's drawback is that it necessitates an equilibration period, requiring the user to take a 60-minute break before beginning any readings [53].

7. Reverse Iontophoresis:
The principle behind reverse iontophoresis is the passage of a small electrical current between a surface-mounted anode and cathode. Ions of sodium and chloride migrate from under the skin toward the anode and cathode, respectively, when an electric potential is supplied between the anode and cathode. Specifically, the current is mostly produced by sodium ion movement [54]. Numerous NGM devices, including GlucoWatch from Cygnus Inc. in the USA and Glu-Call from KMH Co., Ltd. in South Korea, have made extensive use of it.

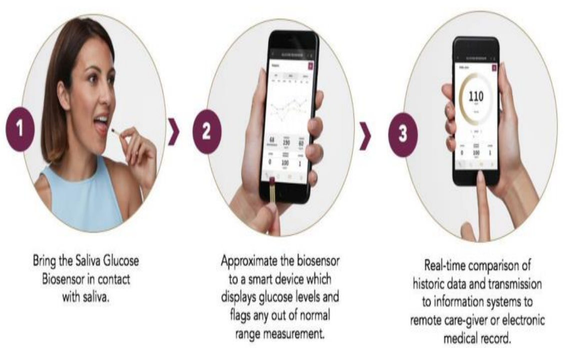
8. Ultrasound:
Using a piezoelectric transducer to produce 20 kHz ultrasound, the method—also called Sonophoresis—increases the skin's permittivity to interstitial fluid and moves glucose to the epidermis, where it is detected using a traditional electrochemical sensor. The concentration of glucose in the interstitial fluid was measured in vivo in rat experiments [55]. Low-frequency ultrasound, which permeates the skin to monitor blood glucose, is the foundation of ultrasound technology. Although there is theoretical potential for this strategy, it appears that no additional research has been conducted since Lee's group published their laboratory findings on rat skin [56]. A variant known as photoacoustic spectroscopy is in use; it relies on stimulating a fluid with a laser light and detecting the acoustic response that results [57].

9. Metabolic Heat Conformation:
In order to determine the blood glucose levels, measurements of heat generation, blood flow rate, haemoglobin, and oxyhaemoglobin concentrations are made [58]. However, because of its high likelihood of influencing the surrounding circumstances, it is only utilized as a supplementary method for measuring glucose. The ambient room temperature, background radiation, and fingertip temperature were all measured in the initial testing. To enhance glucose readings, multiwavelength spectroscopy at different wavelengths (470 nm, 535 nm, 660 nm, 810 nm, 880 nm, and 950 nm) was also employed. Based on this method, Hitachi is attempting to enhance the functionality of a produced glucose sensor prototype [59].

NON-INVASIVE GLUCOSE MONITORING BASED OF BIO-FLUIDS (SALIVA, TEAR AND SWEAT)
1. Saliva-Based Glucose Monitoring:
A mouthguard-style saliva non-invasive glucose sensor is often composed of non-toxic and biocompatible materials [60]. Saliva is a well-known biofluid that is transparent and sticky and is released into the mouth by salivary glands. Numerous indicators are present in it, including glucose, phosphate, lactic acid, enzymes like amylase, hormones like cortisol and steroids, antibodies, and more [61]. One of the main benefits of saliva-based glucose monitoring is that saliva is simpler to extract and gather than other biofluids. Additionally, because

of its richness and ease of use, saliva biomarkers can be studied more easily. A disposable saliva Nano-biosensor was created by Zhang et al. to detect saliva in vitro [62].

While saliva presents a somewhat appealing option for non-invasive blood glucose monitoring, there are still major challenges in the actual detection procedure. Most importantly, it will significantly impede the extraction, detection, and sensing of target analytes, since food residue degradation may result in the formation of numerous secreted proteins, active compounds, and other interfering contaminants during continuous monitoring [61]. High specificity should be maintained by saliva-based sensors in this intricate and dynamic chemical environment [63].

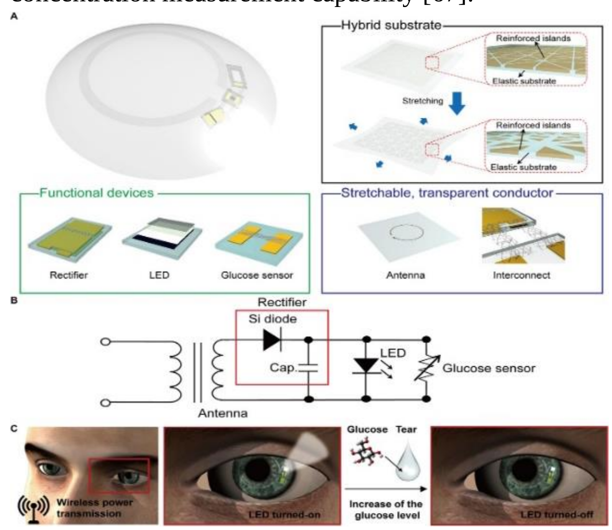



img. 7: Glucose Saliva sensor [64]

2. Tear-Based Glucose Monitoring:

Tears are a biomarker-rich fluid that is high in glucose, protein, salt, and enzymes. Analysing the chemical makeup of the eyes and other body components could provide some helpful information about their health. Tear-based non-invasive glucose sensors have two key advantages: the glucose in tears has a favourable correlation with blood glucose and there are less interfering contaminants in tears [65]. Originally intended to be strips linked to a flexible, stretchy substrate, tear-based glucose sensors have been phased out due to their challenging attachment to the pupil [63].

For user portability and sustainability of glucose monitoring, a lot of research teams are currently concentrating on contact lens-type glucose sensors. It has a wide market potential and not only enables non-invasive continuous detection, but it can also wirelessly transfer real-time data to the user's mobile terminal, making it easy for both doctors and patients to monitor and control blood glucose levels. But there are still a lot of issues with the contact lens-style tear glucose sensor, and it hasn't gotten to the point where it's ready to be sold [66]. Park et al. recently created a flexible smart contact lens that incorporated a wireless display and graphene glucose sensor on an elastic composite substrate. They did this by using a silver nanofiber spinning network as a transparent stretchy circuit. Despite the lens's 93% visible light transparency, 1.3 s response time, 12.57micron detection limit, and heat-optimized design, the gadget regrettably lacks a quantitative tear glucose concentration measurement capability [67].




img. 8: Soft, smart contact lenses [68]

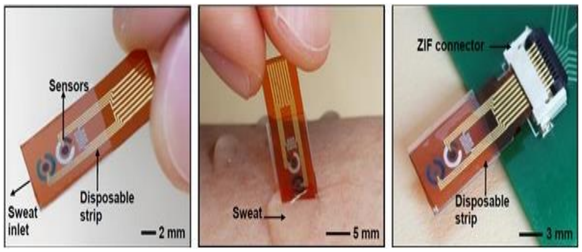
3. Sweat-Based Glucose Monitoring:

Among the most researched types of sensors in recent years is the non-invasive sweat-based glucose sensor. The biological fluid known as sweat is secreted by sweat glands and comprises biological macromolecules, electrolytes, metabolites, and trace elements. Sweat is a hot medium for non-invasive monitoring because it contains blood-related indicators. The patch or band-type's wearable and continuous design allows for the potential for intelligent closed-loop treatment and continuous blood glucose monitoring when combined with other drug-delivery modules. A wearable sweat-based glucose monitoring device with a multistage transdermal medication delivery module was created by Lee et al [69].

Advantages:

The primary benefit of non-invasive sweat-based glucose sensors is the ease with which sweat may be collected. Additionally, most of these wearable, highly integrated devices are pleasant for the human body and capable of continuous measurement.

Limitations:
The main factors limiting its utilization are its relatively poor sensitivity (since sweat contains less glucose) and some hysteresis in relation to blood glucose concentration [70-72].




img. 9: Sweat-Based Glucose Monitoring Device [73]

## CONCLUSION

In this review, the latest technologies and devices for non-invasive glucose monitoring have been described, various technologies which are used in the detection of glucose by non-invasive methods are analysed by their advantages and limitations. Non-invasive glucose monitoring technologies show great promise in transforming diabetes management by offering a more comfortable and convenient method for glucose monitoring. This review also provides a comprehensive overview of the current state of non-invasive glucose monitoring devices and technologies, with a focus on glucose detection in saliva, sweat, and tears.

## REFERENCE


1. Bruen, D.; Delaney, C.; Florea, L.; Diamond, D. Glucose Sensing for Diabetes Monitoring: Recent Developments. Sensors 2017, 17, 1866. [CrossRef]
2. Gamble, J.M.; Clarke, A.; Myers, K.J.; Agnew, M.D.; Hatch, K.; Snow, M.M.; Davis, E.M. Incretin-based medications for type 2 diabetes: An overview of reviews. Diabetes Obes. Metab. 2015, 17, 649–658. [CrossRef]
3. International Diabetes Federation. Foreword. IDF Diabetes Atlas. Brussels, Belgium: International Diabetes Federation; 2011. Available from:http://www.idf.org/diabetesatlas/5e/foreword. Accessed April 10, 2012.
4. American Diabetes Association. Standards of medical care in diabetes – 2012. Diabetes Care. 2012;35(Suppl 1):S11–S63.
5. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014, 37 (Suppl. 1), S14–S80. [CrossRef]
6. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010, 33 (Suppl. 1), S11–S61. [CrossRef]
7. Siddiqui, S.A.; Zhang, Y.; Lloret, J.; Song, H.; Obradovic, Z. Pain-Free Blood Glucose Monitoring Using Wearable Sensors: Recent Advancements and Future Prospects. IEEE Rev. Biomed. Eng. 2018, 11, 21–35. [CrossRef]
8. Bazaev, N.A.; Masloboev, I.P.; Selishchev, S.V. Optical methods for noninvasive blood glucose monitoring. Med. Tekh. 2011, 29–33. [CrossRef]
9. International Diabetes Federation (IDF) diabetes atlas (2015) Brussels, Belgium: International Diabetes Federation.
10. Ong WM, SS Chua, CJ Ng (2014) Barriers and facilitators to self-monitoring of blood glucose in people with type 2 diabetes using insulin: a qualitative study. Patient Prefer Adherence 8: 237-246.
11. Tierney MJ, JA Tamada, RO Potts, RC Eastman, K Pitzer, et al. (2000) The GlucoWatch® biographer: a frequent, automatic and noninvasive glucose monitor. Ann Med 32(9): 632-641.
12. https://images.app.goo.gl/qUzVWws5fvDXGNKa9
13. Wentholt IME, JBL Hoekstra, A Zwart and JH DeVries (2005) Pendra goes Dutch: lessons for the CE mark in Europe. Diabetologia 48(6): 1055-1058.
14. Amir O, D Weinstein, S Zilberman, M Less, D Perl-Treves, H Primack, et al. (2007) Continuous noninvasive glucose monitoring technology based on“occlusion spectroscopy.” J Diabetes Sci Technol 1(4): 463- 469.
15. https://images.app.goo.gl/RnRbHERJ7iAtk9SH9
16. ] Kosir S. 2016. New ways for monitoring diabetes [Internet]. Munich (Germany): WT | Wearable Technologies; 2016 Jul 19 [cited 2017 Feb 11]. Available from: https://www.wearable-technologies.com/2016/07/new-waysfor-monitoring-diabetes/.

17. https://images.app.goo.gl/r52SXMLv3uXLb5xb6
18. Lipson J, J Bernhardt, U Block, WR Freeman, R Hofmeister, et al. (2009) Requirements for calibration in noninvasive glucose monitoring by Raman spectroscopy. J Diabetes Sci Technol 3(2): 233-241.
19. https://images.app.goo.gl/nV1MuJ3LrQfgAWTz7
20. https://images.app.goo.gl/sbFnDMUPVXcPS87FA
21. Aggidis AGA, JD Newman, GA Aggidis (2015) Investigating pipeline and state of the art blood glucose biosensors to formulate next steps. Biosens Bioelectron 74: 243-262
22. Acciaroli G, M Vettoretti, A Facchinetti, G Sparacino, C Cobelli (2016) From Two to One Per Day Calibration of Dexcom G4 Platinum by a Time-Varying Day-Specific Bayesian Prior. Diabetes Technol Ther 18(5): 472-479.
23. Amir O, D Weinstein, S Zilberman, M Less, D Perl-Treves, H Primack, et al. (2007) Continuous noninvasive glucose monitoring technology based on“occlusion spectroscopy.” J Diabetes Sci Technol 1(4): 463- 469.
24. Wentholt IME, JBL Hoekstra, A Zwart and JH DeVries (2005) Pendra goes Dutch: lessons for the CE mark in Europe. Diabetologia 48(6): 1055-1058.
25. Salam NABA, WH bin M Saad, ZB Manap, F Salehuddin (2016) The Evolution of Non-invasive Blood Glucose Monitoring System for Personal Application. J Telecommun Electron Comput Eng JTEC 8(1): 59-65.
26. Cengiz E and WV Tamborlane (2009) A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther 11(1): S11-S16
27. Groenendaal W, G von Basum, KA Schmidt, PA Hilbers, NA van Riel (2010) Quantifying the composition of human skin for glucose sensor development. J Diabetes Sci Technol 4(5): 1032-1040.
28. García-Guzmán J, González-Viveros N, Cerecedo-Núñez H. 2015. Comparative analysis of optoelectronic properties of glucose for non-invasive monitoring. In: Martínez-García A, Furlong C, Barrientos B, Pryputniewicz R. Emerging Challenges for Experimental Mechanics in Energy and Environmental Applications, Proceedings of the 2015 5th International Symposium on Experimental Mechanics and 9th Symposium on Optics in Industry (ISEM-SOI); 2017; p 55-63.
29. Facchinetti A. 2016. Continuous glucose monitoring sensors: past, present and future algorithmic challenges. Sensors. 2016 Dec 9;16(12):2093.
30. Vashist SK (2012) Non-invasive glucose monitoring technology in diabetes management: a review. Anal Chim Acta 750: 16-27.
31. do Amaral CEF, B Wolf (2008) Current development in non-invasive glucose monitoring. Med Eng Phys 30(5): 541-549.
32. https://images.app.goo.gl/TuaxquHGf9Z7KdSf6
33. Diabetes test nixed. USA Today, 27 February 1996: Sect. D, p. 1
34. Chung H, Arnold MA, Rhiel M, Murhammer DW: Simultaneous measurements of glucose, glutamine, ammonia, lactate, and glutamate in aqueous solutions by nearinfrared spectroscopy. Appl Spectrosc 50:270-276, 1996
35. Heise HM, Bittner A, Marbach R. Clinical chemistry and near infrared spectroscopy: technology for non-invasive glucose monitoring. J Near Infrared Spec. 1998;6(4):349–359.
36. Heise HM, Marbach R. Human oral mucosa studies with varying blood glucose concentration by non-invasive ATR-FT-IR-spectroscopy. Cell Mol Biol (Noisy-le-grand). 1998;44(6):899–912.
37. Siesler HW, Ozaki Y, Kawata S, Heise HM. Near-Infrared Spectroscopy: Principles, Instruments, Applications. Weinheim: Wiley-VCH; 2002.
38. Mazarevica, G.; Freivalds, T.; Jurka, A. Properties of erythrocyte light refraction in diabetic patients. J. Biomed. Opt. 2002, 7, 244–247. [CrossRef]
39. Maruo, K.; Tsurugi, M.; Jakusei, C.; Ota, T.; Arimoto, H.; Yamada, Y.; Tamura, M.; Ishii, M.; Ozaki, Y. Noninvasive blood glucose assay using a newly developed near-infrared system. IEEE J. Sel. Top. Quantum Electron. 2003, 9, 322–330. [CrossRef]
40. Vonlilienfeldtoal H, Weidenmuller M, Xhelaj A, Mantele W. A novel approach to non- invasive glucose measurement by mid-infrared spectroscopy: the combination of quantum cascade lasers (QCL) and photoacoustic detection. Vib Spectrosc. 2005;38(1–2):209–215.

41. Brancaleon L, Bamberg MP, Sakamaki T, Kollias N. Attenuated total reflection-Fourier transform infrared spectroscopy as a possible method to investigate biophysical parameters of stratum corneum in vivo. J Invest Dermatol. 2001;116(3):380–386.
42. D.I. Ellis, R. Goodacre, Analyst 131 (2006) 875–885.
43. A. Ergin, G.A. Thomas, Chapter title, in: 31st IEEE Annual Northeast Bioengineering Conference, Hoboken, April 2–3, 2005, pp. 246–247.
44. Berger AJ, Koo TW, Itzkan I, Horowitz G, Feld MS. Multicomponent blood analysis by near-infrared Raman spectroscopy. Appl Opt. 1999; 38(13):2916–2926.
45. R. Badugu, J.R. Lakowicz, C.D. Geddes, Cur. Opin. Biotechnol. 16 (2005) 100–107.
46. T.J. Allen, B.T. Cox, P.C. Beard, Proc. SPIE 5697 (2005) 233–242.
47. Pickup JC, Hussain F, Evans ND, Rolinski OJ, Birch DJ. Fluorescence-based glucose sensors. Biosens Bioelectron. 2005;20(12): 2555–2565.
48. R. Fusman, R. Rotstein, K. Elishkewich, D. Zeltser, S. Cohen, M. Kofler, Acta Diabetol. 38 (2001) 129–134.
49. Moschou EA, Sharma BV, Deo SK, Daunert S. Fluorescence glucose detection: advances toward the ideal in vivo biosensor. J Fluoresc. 2004;14(5):535–547.
50. T.A. Hillier, R.D. Abbott, E.J. Barrett, Am. J. Med. 106 (1999) 399–403.
51. I. Ermolina, Y. Polevaya, Y. Feldman, Eur. Biophys. J. 29 (2000) 141–145.
52. Y. Polevaya, I. Ermolina, M. Schlesinger, B.Z. Ginzburg, Y. Feldman, Biochim. Biophys. Acta 1419 (1999) 257–271.
53. Caduff A, Hirt E, Feldman Y, Ali Z, Heinemann L. First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system. Biosens Bioelectron. 2003;19(3):209–217.
54. Sieg A, Guy RH, Delgado-Charro MB. Noninvasive glucose monitoring by reverse iontophoresis in vivo: application of the internal standard concept. Clin Chem. 2004;50(8):1383–1390.
55. S. Lee, V. Nayak, J. Dodds, M. Pishko, N.B. Smith, Ultrasound Med. Biol. 31 (2005) 971–977.
56. Lee S, Nayak V, Dodds J, Pishko M, Smith NB. Glucose measurements with sensors and ultrasound. Ultrasound Med Biol. 2005;31(7):971–977.
57. MacKenzie HA, Ashton HS, Spiers S, et al. Advances in photoacoustic noninvasive glucose testing. Clin Chem. 1999;45(9):1587–1595.
58. O.K. Cho, Y.O. Kim, H. Mitsumaki, K. Kuwa, Clin. Chem. 50 (2004) 1894–1898.
59. J.B. Ko, O.K. Cho, Y.O. Kim, K. Yasuda, Diab. Care 27 (2004) 1211–1212.
60. Lee, H.; Hong, Y.J.; Baik, S.; Hyeon, T.; Kim, D.H. Enzyme-Based Glucose Sensor: From Invasive to Wearable Device. Adv. Healthcare Mater. 2018, 7, e1701150.
61. Malon, R.S.; Sadir, S.; Balakrishnan, M.; Corcoles, E.P. Saliva-based biosensors: Noninvasive monitoring tool for clinical diagnostics. BioMed Res. Int. 2014, 2014, 962903.
62. Zhang, W.; Du, Y.; Wang, M.L. Noninvasive glucose monitoring using saliva nano-biosensor. Sens. Bio-Sens. Res. 2015, 4, 23–29.
63. Yang, Y.; Gao, W. Wearable and flexible electronics for continuous molecular monitoring. Chem. Soc. Rev. 2019, 48, 1465–1491.
64. https://images.app.goo.gl/tSR1VCo516y7siir7
65. Reid, R.C.; Minteer, S.D.; Gale, B.K. Contact lens biofuel cell tested in a synthetic tear solution. Biosens. Bioelectron. 2015, 68, 142–148.
66. Kownacka, A.E.; Vegelyte, D.; Joosse, M.; Anton, N.; Toebes, B.J.; Lauko, J.; Buzzacchera, I.; Lipinska, K.; Wilson, D.A.; Geelhoed-Duijvestijn, N.; et al. Clinical Evidence for Use of a Noninvasive Biosensor for Tear Glucose as an Alternative to Painful Finger-Prick for Diabetes Management Utilizing a Biopolymer Coating. Biomacromolecules 2018, 19, 4504–4511.
67. Sealy, C. Glucose monitoring in sweat and tears no stretch for new biosensors. Nano Today 2018, 19, 1–2.
68. https://images.app.goo.gl/KATPpfBRXmXUaevv8
69. Lee, H.; Song, C.; Hong, Y.S.; Kim, M.S.; Cho, H.R.; Kang, T.; Shin, K.; Choi, S.H.; Hyeon, T.; Kim, D.H. Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. Sci. Adv. 2017, 3, e1601314.

70. Gao, W.; Ota, H.; Kiriya, D.; Takei, K.; Javey, A. Flexible Electronics toward Wearable Sensing. Acc. Chem. Res. 2019, 52, 523–533.
71. Bandodkar, A.J.; Gutruf, P.; Choi, J.; Lee, K.; Sekine, Y.; Reeder, J.T.; Jeang, W.J.; Aranyosi, A.J.; Lee, S.P.; Model, J.B.; et al. Battery-free, skin-interfaced microfluidic/electronic systems for simultaneous electrochemical, colorimetric, and volumetric analysis of sweat. Sci. Adv. 2019, 5, eaav3294.
72. Kim, J.; Sempionatto, J.R.; Imani, S.; Hartel, M.C.; Barfidokht, A.; Tang, G.; Campbell, A.S.; Mercier, P.P.; Wang, J. Simultaneous Monitoring of Sweat and Interstitial Fluid Using a Single Wearable Biosensor Platform. Adv. Sci. (Weinh) 2018, 5, 1800880.
73. https://images.app.goo.gl/7Y9iqrdJstSVAgCU7