Continuous Blood Glucose Monitoring Techniques: A Review

NMS Irugalbandara[1#] and IMCWB Kohombakadawala

[1]*Faculty of Engineering, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka.*
[#] <mindula.irugalbandara@gmail.com>

Abstract— *Continuous Glucose Monitoring (CGM) is recommended over conventional self-blood glucose monitoring because Continuous Blood Glucose Monitoring has become very essential in Diabetes management. Diabetes / Diabetes mellitus is a chronic disease that has become a major health issue globally. Mainly, Type 1 Diabetes and Type 2 Diabetes need Continuous Glucose Monitoring for disease management. The minimally invasive method is the main technique used for Continuous Glucose Monitoring in the present day. Continuous Glucose Monitoring using non-invasive methods is an emerging field nowadays because of the difficulties related to the existing Continuous Glucose Monitoring methods/systems. This review article presents the importance of Continuous Glucose Monitoring, the existing techniques of Continuous Glucose Monitoring and their new approaches, the difficulties and drawbacks related to them, and the emerging techniques of Continuous Glucose Monitoring. The conclusion states that there is an enormous need for a wearable, inexpensive, non-invasive Continuous Glucose Monitoring approach that has the same accuracy level as the invasive procedures to be used in Diabetes management.*

Keywords— **Continuous Glucose Monitoring, Diabetes, Invasive, Minimally invasive, Non-invasive**

I. INTRODUCTION

Diabetes, often known as diabetes mellitus, is a chronic illness that has gained great worldwide health concern. Diabetes is the third leading cause of death in many developed countries (V K *et al.*, 2020). Continuous Blood Glucose Monitoring is greatly wanted for patients with complex medical problems, type – 1 diabetes and violent types of type-2 diabetes so that unexpected fluctuations in blood glucose levels, which are known to cause death due to abrupt hypo-glycemia during sleep, can be caught. Ultimate blood sugar swings have been linked to cardiovascular problems and even fatalities. Therefore, it is important to for them to monitor blood glucose levels continuously. The use of Continuous Glucose Monitoring (CGM) devices can help to detect the excessive blood sugar swings and notify the patient, improving self or parental management and reducing the risk of serious hypo or hyper-glycemia-related consequences (Malik *et al.*, 2023).

II. DIABETES/DIABETES MELLITUS

Diabetes/Diabetes Mellitus is a condition in which the body is unable to create enough or any insulin, to use the produced insulin appropriately (cells do not respond to the produced insulin), or to perform a combination of the two. The body is unable to transport sugar from the blood into your cells when any of these things take place. Then it will cause high blood sugar levels (Narkhede, Dhalwar and Karthikeyan, 2016). It may cause kidney damage (nephropathy), nerve damage (neuropathy), eye difficulties (retinopathy), infection or skin disorders, artery disease that can cause heart attack or stroke, amputations due to neuropathy or vascular disorders, etc. (Yadav *et al.*, 2014), (Kim *et al.*, 2022).

There are three categories of diabetes mellitus, as type 1 which is Insulin-dependent, type 2 which is Non-insulin-dependent and gestational diabetes (diabetes while pregnant) (V K *et al.*, 2020), (Reddy P and Jyostna K, 2017). Type 1 diabetes mellitus is the most hazardous form. It affects between 5–10% of those who have the disease. The immune system's destruction of the beta cells produced in the pancreas, which stops the body from making adequate insulin, is the main cause of it. Due to the fact that pancreatic damage is irreversible, patients with this disease must either inject insulin or wear an insulin pump in a daily basis (Hu and Li, 2016). It typically takes place between childhood and adolescence (Reddy P and Jyostna K, 2017). Currently, there is no prevention for type 1 diabetes. There isn't any conclusive information regarding the incident or circumstances that causing type 1 diabetes (Lema-Perez L, Aguirre-Zapata E and Garcia-Tirado J, 2015). The most widespread form of diabetes is type 2 diabetes mellitus. The majority of diabetics (90–95%) are type 2. It mostly happens when the body produces too much insulin, when the body does not correctly use the insulin, or when an insulin-induced response from the cell is absent. It typically manifests in overweight and grown-up people (Reddy P and Jyostna K, 2017). A genetic predisposition and the so-called western lifestyle, in which people are habituated to a high-carbohydrate diet and little to no exercise, are the main causes of Type 2 Diabetes (Lema-Perez L, Aguirre-Zapata E and Garcia-Tirado J, 2015). Via changes in a healthy way of life, such as decreasing weight, eating a nutritious diet, exercising, etc., type 2 diabetes can be controlled, prevented, or delayed. Several drugs are used to treat it in order to assist control blood sugar levels. The third kind of diabetes mellitus is gestational diabetes. The majority of the time, it takes place when increased blood sugar levels are developed in pregnant ladies who have never had diabetes earlier (Reddy P and Jyostna K, 2017). Type 2 diabetes develops in about 50% of those who are diagnosed with gestational diabetes.

Despite sharing a name, Type 1 and Type 2 Diabetes Mellitus have quite different physiopathology and approaches to treatment. Today, early-diagnosed Type 2 Diabetic patients can be managed with a consistent dose of weekly exercise and a nutritious diet. On the other hand, Type 1 Diabetic patients must follow a tight regimen of Continuous Glucose Monitoring in addition to daily insulin injections. They must also engage in continuous physical activity and consume a nutritious diet, just like Type 2 Diabetic patients (Lema-Perez L, Aguirre-Zapata E and Garcia-Tirado J, 2015).

III. BLOOD GLUCOSE LEVELS

A healthy person's blood sugar concentration varies from 70 to 100 mg/dl when they are abstaining in food, and it increases to 120 to 140 mg/dl after eating a meal high in carbohydrates (V K *et al.*, 2020).

The three primary classifications of blood sugar levels are hyper-glycemia (high blood sugar level), normal blood sugar level, and hypo-glycemia (low blood sugar level). For children, the normal blood glucose range is 70 mg/dl to 100 mg/dl, while for grown-ups, it is 70 mg/dl to 150 mg/dl. When the blood glucose concentration exceeds 150 mg/dl, it is known as hyper-glycemia, when it falls below 70 mg/dl, it is known as hypo-glycemia (Reddy P and Jyostna K, 2017). Speaking may be challenging due to hypo-glycemia, and it can also make the patients unconscious and put them in a coma (Kumar D and Jayanthy T, 2020).

To live a healthy lifestyle, it's crucial to keep the blood sugar levels adequate. Diabetic patients must regularly, most of the patients continuously monitor their blood glucose levels for appropriate diabetic care (Zeng N *et al.*, 2018). Since, more people are developing diabetes today, it is evident that monitoring blood glucose concentration regularly/continuously is necessary (Dinh *et al.*, 2020).

IV. BLOOD GLUCOSE MONITORING

Blood glucose monitoring is done mainly in three types of methods as invasive, minimally invasive and non-invasive methods. The invasive type is the abundantly used and conventional technique (Dinh *et al.*, 2020).

A. Invasive method

The Hexokinase Method is the benchmark for estimating blood glucose levels. Using specialized laboratory equipment, a 1.5 ml blood sample will be extracted during this operation. This approach cannot be used in a home context, is not real-time, or portable. Because of this, the most popular strategy for managing diabetes successfully and effectively has come to rely on an invasive finger-pricking approach. This uses glucometers, in which an electrochemical test strip communicates with a blood drop drawn from the finger prick (Laha *et al.*, 2022).

B. Minimally invasive method

In this method a periodic subcutaneous implanting of a component(metal) which serves as a sensor should be done. The majority of the sensors are electrochemical sensors which release oxidizing enzyme that breaks down blood sugar. When the enzyme interacts with blood sugar particles, among other substances, hydrogen peroxides are formed. A current is also produced as a result of the reaction. By detecting the charge on this current, one can determine the proper level of blood sugar in the interstitial cells (Laha *et al.*, 2022). This is the most popular method used in Continuous Glucose Monitoring.

C. Non-invasive method

There are many non-invasive methods which are developed to monitor the blood glucose concentration in order to avoid the difficulties related to the invasive and minimally invasive methods. Although no blood (or other fluid) is used in non-invasive (NI) glucose testing, obtaining very accurate values is the key concern (Harman-Boehm *et al.*, 2009). Non-invasive glucose monitoring has a big ability to help manage diabetes effectively (Lin, 2017). There are many techniques which are used to monitor the blood glucose concentration non-invasively. Optical, transdermal, and thermal approaches are instances for techniques utilized for non-invasive glucose monitoring. The various properties of light are used in optical technologies to modify glucose in a way that depends on concentration. Transdermal methods test glucose via the skin by using ultrasound or electricity. Last but not least, thermal approaches aim to assess glucose by locating physiological markers related to metabolic heat production (Lin, 2017).

Under optical technologies there are methods such as near-infrared absorption spectroscopy, mid-infrared absorption spectroscopy, raman spectroscopy, photoacoustic spectroscopy, radio wave spectroscopy, fluorescence (Lin, 2017), (Kumar D and Jayanthy T, 2020), optical polarimetry, Surface Plasmon Resonance and optical coherence tomography (Laha *et al.*, 2022). Impedance spectroscopy, reverse iontophoresis and ultrasound (Harman-Boehm *et al.*, 2010) are methods related to transdermal technology. Metabolic heat conformation and conservation of energy are methods of thermal technology used in non-invasive glucose monitoring (Kumar D and Jayanthy T, 2020), (Lin, 2017).

In addition to the above-mentioned techniques there are few methods which are used for non-invasive blood glucose monitoring such as electromagnetic sensing and nanomaterial-based sensing. Electromagnetic sensing can be further separated into two methods as planar microwave resonant sensors and antenna sensing based on the equipment used and the principles of microwave physics. In addition to the methods already stated, few other methods such as nuclear magnetic resonance has also been researched. Some studies are done about sensors integrating three different types of non-invasive glucose measurement technologies (Laha *et al.*, 2022). Most of these methods are being researched to use for Continuous Glucose Monitoring.

V. CONTINUOUS BLOOD GLUCOSE MONITORING

Continuous blood glucose monitoring is a method used to continuously monitor blood sugar levels throughout the whole day.

Even though the invasive method produces accurate results in almost every case of blood glucose monitoring, it cannot be used for Continuous Glucose Monitoring (Sreenivas C and Laha S, 2019) because continuous finger pricking causes pain, discomfort, and the risk of infection while being inconvenient to the patients because of the disruptions to their daily activities. Providing only intermittent data, which misses crucial glucose fluctuations between tests, has also become a drawback of this method. Therefore, minimally invasive and non-invasive methods are used/researched for Continuous Glucose Monitoring.

A. Minimally invasive method

This is the existing method for CGM. The creation of implantable minimally invasive biosensors has made it possible to create CGMS – Continuous Glucose Monitoring Systems. Enzyme-based glucose sensors are the most used type of sensors. Instead of using actual blood, a minimally invasive sensor is attached to the body and estimates blood glucose level using interstitial fluid. The benefit of Continuous Glucose Monitoring is that it can foresee potential hypo- or hyper-glycemic episodes and warn the patient (Malik *et al.*, 2023).

Commercial Continuous Glucose Monitoring (CGM) devices, including Dexcom, Adobe FreeStyleLibre, Eversense, and others, have only recently entered the market. The metal that is used in modern CGM is implanted subcutaneously and remains in contact with the blood. The commercial CGMS that are now on the market are beneficial for a few days to a few months because even the sensitivity of enzyme-based glucose sensors is excellent, their durability is low. Therefore, it must be replaced on occasion (Malik *et al.*, 2023).

Although minimally invasive CGM systems have been quite accurate and effective at monitoring blood glucose levels in diabetic patients (mainly insulin-dependent - type 1), there are still significant barriers. These include high costs (specially for the enzyme-based glucose sensors utilizing CGMS because the sensors are not reusable and should be changed in a regular basis), especially for those without insurance or with inadequate insurance, difficulty in placing the devices on the body, and disliking the skin attachment of the subcutaneous implant, especially for adolescents. There are many more disadvantages, including uncomfortable insertion that may necessitate surgery, pain, and a potential risk from the presence of an external object subcutaneously. In some cases, the bonding agents used in CGM devices may potentially cause skin pain and contact dermatitis. These skin issues might negatively impact adherence to CGM and cause emotional anguish in diabetic patients. CGM devices still need a number of finger prick tests each day to calibrate the subcutaneously implanted sensor since they measure blood glucose using interstitial fluids, which is an indirect measurement of BGL and this is another difficulty related to minimally invasive CGM systems (Wilkes R *et al.*, 2018).

There are several studies as follows which have done to minimize these problems.

A study has come up with an electromagnetic sensor which is implantable for Continuous Glucose Monitoring which is long lasting, extremely sensitive, and minimally invasive and can track even the smallest variations in blood glucose concentration. The suggested sensor is a compact electromagnetic based resonator which detects minute dielectric permittivity changes in interstitial fluid (ISF) brought on by variations in blood glucose level using powerful oscillating nearfield (Malik *et al.*, 2023).

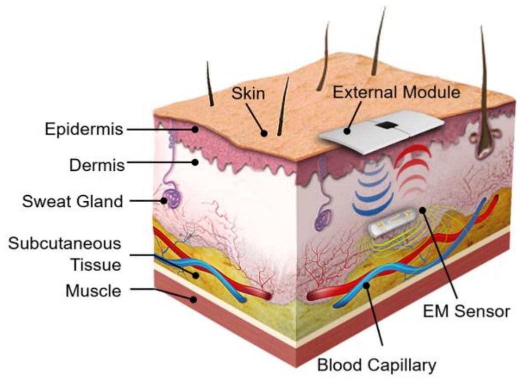

Figure 1. The proposed sensor's conceptual implantation under the skin with an external module linked to the body's exterior surface which is just above the sensor position
Source: (Malik *et al.*, 2023)

In contrast to enzyme-based glucose sensors, the proposed EM-based glucose sensor does not necessitate direct contact with blood or ISF. Instead, the oscillating near field is able to pick up slight changes in the dielectric permittivity of ISF which are caused as a result of variations in glucose levels. Figure 1 shows how the sensor is implanted in the body. The proposed sensor, which can measure glucose level using the nearby ISF, is placed into the dermis. The external module's duties include providing the sensor with power and using backscattered modulation to obtain the resonance frequency data. The ISF glucose level and BGL-Blood glucose level has a strong association. When the BGL changes, the ISF's dielectric constant also changes. The sensor's resonance frequency changes as a result of this. Regression equation is used to obtain the real-time BG level matching to sensor frequency data. The blood capillaries' glucose diffuses to the tissues around the ISF. ISF glucose level and real blood glucose level are thus separated by a time interval. There is frequently a 10–20 minutes lag between the highest BGL and highest ISF glucose levels, depending on the person's health. This time delay is a crucial measure in Continuous Glucose Monitoring Systems (CGMS) for predicting hyper-glycemic or hypo-glycemic warnings (Malik *et al.*, 2023).

The suggested sensor's capacity to monitor BGL was tested on real rats in a licensed clinical setting. It was done using the C57BL/6J mouse and the Sprague Dawley rat in intravenous glucose tolerance tests (IVGTT) and insulin tolerance tests (ITT) respectively. The experimental data demonstrates that the suggested sensor is suited for high precision, long-term CGMS applications. This work is significant because it presents a fresh viewpoint on the creation of a long-term CGM system based on an electromagnetic implant sensor. In this work, tiny variations in BGL cause a large change in the sensor resonance frequency. Therefore, as mentioned in the research paper according to the research team knowledge, this suggested sensor is the first of its kind that can track BGL constantly in real time and is subcutaneously implantable (Malik *et al.*, 2023).

The electromagnetic behaviour of the sensor should not deteriorate with time, according to theory. However, a number of additional factors may also have an impact on sensor performance. For long-term use, the sensor packaging is one crucial element. Even though biofouling, blood clots on sensor, tissue inflammation, and fibrous development around sensor can all seriously impair sensor performance over time which will be an issue (Malik *et al.*, 2023).

A smart-shoe device called the eTac, which can deliver autonomous pseudo-continuous BGM, is shown in another study. The system may be broken down into two components as a disposable cell and a smart-shoe matrix. This study was done because the need for a device that can provide accurate pseudo continuous BGM in a minimally invasive way has become apparent, a device that can facilitate autonomous testing would eliminate many of the issues that diabetics face when trying to test their blood sugar and the development of a wearable BGM system has been constrained by the high energy costs associated with lancet actuation. The research team has concentrated on methods for boosting the volume of blood taken from the induced lancet wound (Wilkes R *et al.*, 2018).

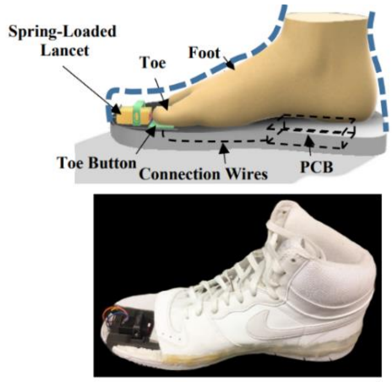

Figure 2. The design of the eTac smart shoe and its prototype
Source: (Wilkes R et al., 2018)

The eTac prototype was tested with the help of two male volunteers. The outcomes of the test show that the eTac regularly extracts more blood than needed compared to the test strip used by the industry, which is 1.2 microliters. The in-vivo testing was also done using the same samples from the two test participants. No volunteers had any lancing pain during the experiment. The results from the tests exhibit the feasibility of the study. Its ability to use readily obtainable energy to actuate the spring-loaded lancet and then provide an indirect oscillating pressure to the resulting skin opening is what makes this concept unique. This technique can be used right away as an autonomous help for CGM systems that need two daily calibrations. Even though, this method is feasible, more future developments and testing are needed for this study (Wilkes R *et al.*, 2018).

B. Non-invasive method

Continuous Glucose Monitoring using non-invasive methods has become the emerging field nowadays because it has become the most convenient method for the patients with less risk, less distruptions and no pain. There are several non-invasive methods which are studied for non-invasive Continuous Glucose Monitoring.

In (Sreenivas C and Laha S, 2019) a functioning prototype of a small, wearable, and reasonably priced continuous non-invasive blood glucose measuring device based on the electromagnetic characteristics of blood glucose has been developed and in-vivo tested with the help of a Bluetooth Low Energy (BLE) based microcontroller kit. The suggested non-invasive monitoring method uses the supplied BLE signal to pass through human tissue (the fingertip) and assess the blood glucose level. This is accomplished by measuring the strength of the received BLE signal's Received Signal Strength Indicator (RSSI). The working model can be used in a wearable form factor and can be used in a reliable, inexpensive way that has not yet been described. This is made feasible by a cutting-edge measurement method that uses RSSI from the BLE signal to check blood glucose without utilizing any intrusive procedures. Human individuals who were fasting underwent the Oral Glucose Tolerant Test (OGTT) by ingesting a 50gm glucose solution. For correlation, data were taken simultaneously using the suggested non-invasive procedures and traditional invasive blood sampling. The proposed inexpensive and wearable prototype's clinical importance is validated by the temporal trend shown on the OGTT protocol from the proposed non-invasive measurement and the invasive blood pricking.

Using two microwave split ring resonators operating at 1.4 GHz, a design for a fully non-invasive Continuous Blood Glucose Monitoring sensor is proposed in (Choi H *et al.*, 2014). Copper wire with a silver coating is used to make the rings. A reference ring is introduced in addition to the sensing ring and works at a higher frequency. This is used to calibrate out any effects brought on by temperature fluctuations and to account for the ring's expansion that is temperature sensitive. The pair of rings that make up the proposed sensor are immediately adhered to the skin of the abdomen using an adhesive patch. A blood glucose strip and a continuous glucose monitor were used to evaluate the proposed sensor together with two other commercially available sensors over the course of 12 hours with three food events. The outcomes from the commercial sensors and those from the blood glucose measurements correlated positively. Since the test subjects did not have diabetes, the study only took into account a narrow range of blood glucose levels.

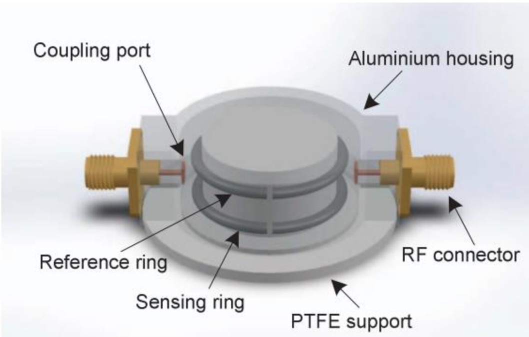

Figure 3. The suggested sensor's proposed 3D construction based on two split-ring resonators
Source: (Choi H *et al.*, 2014)

With the help of a single NIR LED (880 nm), a continuously wearing in-ear non-invasive glucose monitoring device is introduced in (Hammour and Mandic, 2023) as a proof of concept. The authors have considered patients who belong to different diabetes types with blood glucose values ranging from 63 to 345 mg/dL. The proposed device, according to the research report, is the first to use the ear canal as a site for non-invasive glucose measurement in blood using NIR spectroscopy. This opens up possibilities for invisible all-time blood glucose monitoring in the community. When NIR light is emitted through the blood vessels in the ear canal, it interacts with the medium and is reflected. The photoplethysmography (PPG) records pulsed-periodic signals because both scattering and absorption reduce the light's intensity. Blood with a higher glucose percentage will have a different absorbance than blood with a lower glucose concentration, claims PPG. This will alter the structure of the PPG signal, which can then be mapped onto a collection of traits and fed into machine learning algorithms to indirectly forecast the blood sugar level.

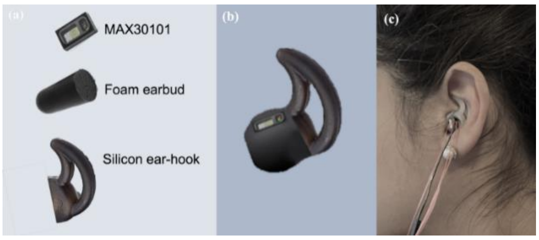

Figure 4. a) Different parts of the in-ear PPG sensor, b) A viscoelastic earbud with a PPG sensor chip inserted in it, is attached to an ear hook, c) Placement of the sensor within the ear canal
Source: (Hammour and Mandic, 2023)

All of the above mentioned studies are in the research domain which are expecting many more future developments.

Despite the clear benefits, many non-invasive techniques have accuracy problems and frequently fail to win FDA approval. Non-invasive technologies have many drawbacks such as the accuracy of indirect glucose monitoring is reduced by the physiological lag between blood and tissue glucose, not being able to be a substitute for the conventional glucometer, calibration against current blood glucose measurements is necessary to estimate the concentration of glucose, usability and applicability challenges (Lin, 2017) etc.

The following table gives a summary of the studies related to Continuous Glucose Monitoring methods.

Table 1. Summary of studies related to CGM methods

CGM method	The study	Reference
Minimally-invaisve	An electromagnetic sensor which is implantable	(Malik *et al.*, 2023)
Minimally-invaisve	The eTac smart shoe	(Wilkes R et al., 2018)
Non-invaisve	A device which has been developed with a Bluetooth Low Energy (BLE) based	(Sreenivas C and Laha S, 2019)

	microcontroller kit	
Non-invasive	A sensor based on a microwave split ring resonator	(Choi H *et al.*, 2014)
Non-invaisve	An in-ear PPG sensor using NIR spectroscopy	(Hammour and Mandic, 2023)

VI. CONCLUSION

Continuous Glucose Monitoring has become very essential for Diabetes management. The existing methods for Continuous Glucose Monitoring have several drawbacks and difficulties that complicate the lives of the diabetic patients. The emerging approaches for CGM are also in the research domain, with the need of future developments and testing. A CGM approach that is non-invasive, wearable, inexpensive, and accurate at a level with traditional invasive procedures is therefore required because of the difficulties related to existing CGM procedures. The development of an efficient method and sensor device to measure BGL precisely and constantly in a non-invasive manner is currently the subject of many active researches. A challenging task in diabetes care has been the development of wearable trustworthy non-invasive Continuous Glucose Monitoring devices that can function for extended periods of time.

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AUTHOR BIOGRAPHIES

NMS Irugalbandara is currently a final year Biomedical Engineering Undergraduate at the Faculty of Engineering of General Sir John Kotelawala Defence University, Sri Lanka. Her final year individual research project is on the Development of a wearable, Non-Invasive Continuous Glucose Level Measuring System that uses Near-infrared spectroscopy.

Mr. IMCWB Kohombakadawala is a probationary lecturer in the Biomedical Engineering degree program at the Department of Electrical, Electronic, and Telecommunication Engineering at General Sir John Kotelawala Defence University, Sri Lanka. His subject and research areas include Medical instrumentation and Medical imaging.