



A Review on Continuous Glucose Monitoring (CGM): Perspectives on Glucose Biosensors

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ABSTRACT

This review highlights the need for continuous monitoring devices (CGM) in comparison with the self-monitoring of blood glucose (SMBG), with a little focus on various marketed CGM devices. It provides significant attention to the latest generations of glucose biosensors and enzymatic glucose bio sensing. The advantages and limitations of various physiological samples for continuous glucose monitoring are discussed. Also, discussed are the use of semipermeable membranes to improve the biosensor's sensitivity and selectivity while retaining its stability.

Keywords: Continuous Glucose Monitoring, Glucose Oxidase, Interstitial Fluid, Self-Monitoring of Blood Glucose
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INTRODUCTION

Diabetes Mellitus (DM) is a common endocrine metabolic disorder distinguished by chronic hyperglycemia resulting from malfunction in the metabolism of proteins, carbohydrates, and fats.¹⁻³ It is due to ineffective production and action of insulin hormone which either increase or decrease the concentration of glucose. It cause damage, dysfunction, and organ failure over the long term, particularly to the heart, kidneys, eyes, nerves, and blood vessels.² DM is primarily divided into two types: Type I insulin-dependent diabetes and Type II non-insulin-dependent diabetes (NIDDM, Type II). A localized inflammatory response in and around the islets of Langerhans cells, followed by the selective death of insulin-secreting cells, characterizes type I diabetes, an autoimmune illness. T2 DM is characterized by decreased insulin secretion and peripheral insulin resistance.⁴ The International Diabetes Federation (IDF) predicted that by 2025, there will be 69.9 million people worldwide who have diabetes.⁵

Better Blood Pressure (BP), cholesterol, and glycemic control are the objectives of diabetes management. HbA1c values are used to calculate glucose levels, which is the illustration of the percentage of all glycated hemoglobin during the last three months. It is FBS (fast blood sugar) in patients and does not require fasting prior to testing and also serves as a marker for detection of various micro vascular complications.² The standards for FBG were set by WHO for patients with diabetes has ≥ 7.0 mM FBG, 2 hours after a meal ≥ 11.1 mM and for normal people at 3.9 to 6.1 mM, 2 hours after a meal at 7.8 mM or less. An oral hypoglycemic medication or insulin therapy is a common complication of hypoglycemia, which is a condition where blood glucose levels are below 3.9 mM and last for around 5 minutes. As the risk coefficient is even larger in elderly patients and at night, it is difficult to monitor this condition with traditional blood glucose detection method. Therefore, continuous glucose monitoring (CGM) has more clinical application and value in present market trends.⁶

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With significant advancements in precision, dependability, and also convenience, a large group of patients adopted CGM devices for their daily self-management. Unlike to the traditional self- monitoring of blood glucose (SMBG), CGM provides data regarding current blood sugar levels, glucose trends, and the speed and direction of those changes through arrows. It allows the patients to make decision in calculating insulin medication and factors impacting their glycemic control. Continuous glucose monitoring (CGM) is a newer technology for assessing treatment efficacy, safety in patients with Type I and selected patients of Type II.⁷ Generally, patients with T1D need to test their Blood glucose level atleast 4 times a day and in case of pregnant woman as many as 10 times a day. People who are under treatment of Oral medications, insulin especially in T2D certain medications causes hypoglycemia. In all such conditions CGM is recommended.

CGM measures interstitial glucose levels as a way to optimize the levels in the target range for a longer time period their by improving HbA 1C.⁸ Continuous Glucose Monitoring (CGM) systems are divided in to two main categories 1) Professional CGM Devices 2) Personal Systems. Professional CGM systems are referred to use by the patients provided by their health care provider's. After a short period of time, they will return to the clinic and the data can be download and analyzed. It is used to assets the patient's in achieving there glycemic target and also to improve their physical activity which includes Freestyle Libre Pro, Medtronic iPro 2.^{9,10} Where, Personal systems are used for both Real-time observations and retrospective review of complete profile of patients. Personal rtCGM device continuously transmit the glucose data to receiver or smartphone, and isCGM displays a glucose reading every time the handheld reader I s scanned over the sensor. Only 5 CGM sensors are stand-alone marketed, from which four of those sensors are referred to as real-time

CGM systems (rtCGM) i.e., Medtronic Guardian Connect Sensor, Eversense sensor, Dexcom G5 Sensor and Dexcom G6 sensor and only one is intermittently scanned CGM FreeStyle Sensor.¹¹

GENERATIONS OF GLUCOSE BIOSENSORS

Leland Clark and Champ Lyons developed first glucose sensor using the Glucose Oxidase enzyme coated by employing semipermeable over the oxygen electrode to select especially β-D- glucose in presence of oxygen gas.¹³

Potential change in electrode is detected based on the amount of consumed oxygen to produce water. Based on the various electron transfer mechanisms electrochemical biosensors are divided into three generations.⁶

First Generation Glucose Biosensor (Classic GOx Electrode)

It calculates the amount of glucose consumed based on the amount of hydrogen peroxide produced or the consumed oxygen in the reaction.

The main advantage of this process is straight-forward and the huge drawback is the requirement of strong potential (more than 1 V) for decomposition of hydrogen peroxide⁶ and it leads to ready oxidization of some of the reductive molecules like uric acid, ascorbic acid, lactic acid and acetaminophen. It significantly reduces the glucose's selectivity and frequently yields inaccurate readings(Figure 1).

Second Generation Glucose Biosensor-(Mediator GOx Electrode)

Mediator GOx Electrode uses redox mediator it directly interacts with enzyme alleviate some of the limitations of first-generation biosensors with enzyme. Where, oxygen is replaced by electrons by electron acceptor which is in contact between electrode surface and the enzyme. Also suffer

Table 1: Marketed continuous glucose monitoring devices⁹⁻¹²

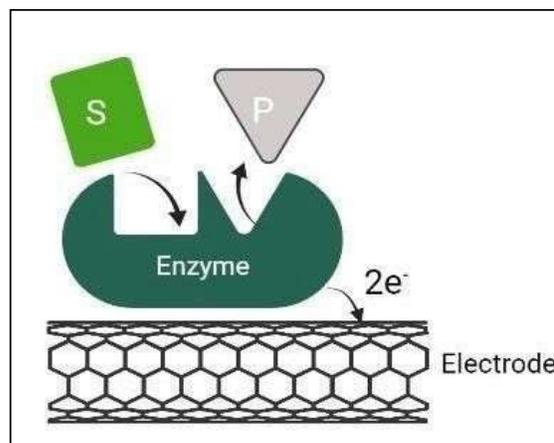
	Professional CGM Devices		Personal CGM Devices			
			Real-time CGM		Flash/Intermittently scanned CGM	
	Freestyle LibrePro	Medtronic iPro2	Medtronic guardian connect sensor	Eversense sensor	DexcomG6 sensor	Free style libre
Type of CGM	Professional CGM	Professional CGM	Personal Real-time CGM	Real-time CGM	Real-time CGM	Flash CGM
Site of application	Upper arm	Abdomen	On Abdomen	Implanted sensor (into upper arm)	On Abdomen	Upper arm
Sensor wear	Up to 14 days	Upto 6 days	Up to 6 days	Up to 90 days	Up to 10 days	Upto 14 days or 10 days
Wear-uptime	1 hour	1 hour	Every 2 hours	24 hours	2 hours	14 days system (1-hour) 10 days system (12 hours)
Frequency of glucose rseadings	Every 15 min	Every 5 min	Every 5 min	-	Every 5 min	Every 15 min
Accuracy	-	-	13.6%	-	9.8%	12.3%

from the interfering species but, can be overcome by using perm selective polymer membrane. These are the chemical substances that transport the electrons from the enzyme's active region to the electrode. Ferrocyanide, thionine, methylene blue, hydroquinone, and ferrocene (Figure 2) are a few examples of the mediators.¹⁴

During the oxidation of glucose, mediators are reduced; these reduced mediators are then further oxidized to produce an output signal.¹⁵ These reduced mediators are again utilized for further reaction process. The current response, response time, and sensitivity of these generation biosensors are shown higher

Third Generation Glucose Biosensor (Direct GOx Electrode)

The consumption of oxygen (First generation), electron mediator (Second generation) affects the selectivity and sensitivity of biosensor. Its aim is to use the direct electron transfer between the enzyme and the electrode^{13,15} in the absence of medium in order to achieve higher sensitivity and fast response speed. It is quite challenging to achieve FAD and redox center must be closer because of its thick protein layer coating over FAD (Figure 3). Intermolecular interactions are enhanced by promoting the electron transfer by fixation



S: Substrate, P: Product

Figure 3: Third Generation Glucose Biosensor (Direct GOx Electrode)

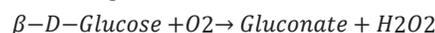
of enzyme over the porous polymer electrode surface which, resulting in excellent electro catalytic activity. It showed improved sensitivity compared to other generations. But the linear detection range is narrow, which is not ideal property.⁶

Methods of Enzymatic Glucose Biosensing

Most glucose assay techniques involve an enzymatic process to produce a quantifiable result that is proportionate to the glucose concentration. There are three most used enzymes in glucose detection.¹⁶

Glucose Oxidase

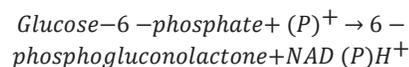
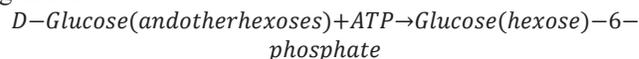
Glucose Oxidase is an enzyme which helps in the conversion of β -Glucose to D- gluconolactone.



Interferences are expected from the strong reducing endogenous agents like Uric acid, bilirubin, glutathione, hemoglobin etc. and also from exogenous chemicals like Acetaminophen, tetracycline, ascorbic acid etc. As enzyme mostly depends on oxygen consumption this method is not useful for blood sample due to varying oxygen levels and red blood cell consumption which results in false glucose results.

Hexokinase

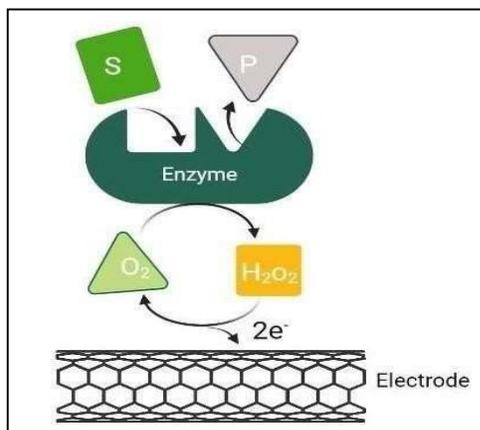
It is the rarely used enzyme exhibits low specificity and will readily accept mannose, and other carbohydrates along with glucose.



This method is also susceptible to interferences due to turbidity, hyperbilirubinemia, hemolysis etc., where interfering chemicals like phosphates are released that prevent the activity of enzymes like hexokinase, glucose-1-phosphate, and fructose-6-phosphate etc.¹⁶

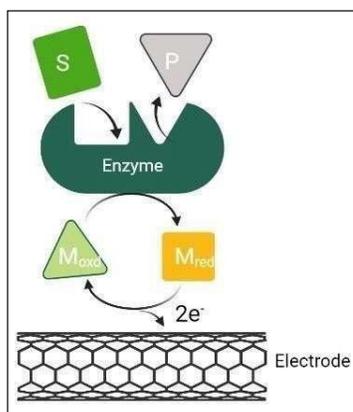
Glucose Dehydrogenase

There are three different glucose dehydrogenases (G-6-phosphate dehydrogenase, glucose-1dehydrogenase, and



S: Substrate, P: Product

Figure 1: First generation Glucose Biosensor (Classic GOx Electrode)



S: Substrate, P: Product

Figure 2: Second generation Glucose Biosensor-(Mediator GOx Electrode)

quinoprotein glucose dehydrogenase) are commonly used in the assay of glucose.¹⁷



It is not just selective for glucose, other sugar molecules like xylose, mannose, galactose interfere the assay.^{16,18}

Continuous Glucose Monitoring in Different Body Fluids

Blood

Blood is the most used physiological fluid for clinical diagnosis because of its reproducibility, sensitivity and affordability of manufacture in large quantities.²³ It includes a variety of proteins (plasma, secreted, foreign proteins etc.), ligand receptors, metabolites, electrolytes etc. which is helpful in correlating disease diagnosis, progression and treatment. This sample is used for self-monitoring generally by using a fingertip puncture which is highly innervated, painful and also fingertips become sore by frequent testing.²⁴ Moving beyond this blood panel of real-time standard for continuous monitoring of proteins and other macromolecules¹⁹ is a major problem.

Urine

Urine is non-invasively collected diagnostic fluid used for diabetes. Composed of many components of metabolites, dissolved salts like glucose, nitrates, proteins, sodium and potassium. It has the pH range in between 4.5–8 (Table 2), because of this intermittent nature and sample collection is also difficult, so it is not incorporated for continuous monitoring.^{21,25}

Sweat

It is one of the most readily available bodily fluid and plays a critical role in thermoregulation. Due to the presence of blood related biomarkers it is used for non-invasive monitoring. A wearable patch design is used for continuous monitoring of glucose. But the challenges faced are difficulty in sample collection, GOx enzyme activity variation and delamination due to mechanical friction etc.²¹ It is not a suitable sample for diabetes diagnosis as it requires longer period of exercise,

ionization stimulation to collect sample for detection. Due to the low concentration of glucose in sweat, there is a poor sensitivity (Figure 4).

Saliva

A mouth-guard type non-invasive glucose sensor is developed using saliva.²⁶ It is a sticky, clear biofluid that includes a number of different biomarkers like phosphate, glucose, hormones like steroid, cortisol's and antibodies and enzymes like amylase etc. which are associated with infection.¹⁹ Although it is a suitable candidate for non-invasive monitoring of glucose but, has many challenges in detection of particles due to release of huge number of active chemicals, impurities and secreted proteins from decomposition of food residues interferes with the continuous monitoring. Moreover, the humidity and temperature conditions will favor biofilm development on the sensor's surface because of bacterial growth and reproduction in the mouth will ultimately reduce its sensitivity. As their no clear understanding between blood and saliva glucose levels. It is very challenging for therapeutic intervention.²¹

Ocular Fluid

Tears is an extracellular complex fluid contains many similar analytes has that of blood and is also called as Aqueous humour,²¹ a biomarker-rich liquid, containing many analytes such as electrolytes, glucose, ascorbic acid, proteins, peptides, hormones, and carbohydrates etc. The main advantage of this sensing technology is that there are only fewer interferences, and the glucose can be positively correlated with the blood glucose. This fluid is investigated for both continuous and non-invasive glucose monitoring. Research is going on to generate glucose smart-contact lens type sensor in terms of continuous monitoring and additionally to send real-time data to users. It is a tiny sensor in which redox reactions are observed by generation of hydrogen peroxide at the working electrode which quantifies the amount of glucose present. As it requires increased transmittance, and wireless power supply which should enough to the eye be in close to function efficiently. It has many advantages in both continuous and non-invasive monitoring where, blinking and tear secretion help in

Table 2: Continuous Glucose monitoring in different Body Fluids

Bodyfluid	Sampling technique	Biomarker	Concentration for healthy patients	Concentration for Diabetic patients	pH
Blood	Needle,Lancet	Glucose	4.9–6.9mM ¹⁹	2–40mM	7.35–7.45
Interstitial Fluid	Micro-dialysis, Iontophoresis, Micro-needle array	Glucose	3.9–6.6mM	1.99–22.2	7.2–7.4
Urine	Passive Collection or catheter	Glucose	2.78–5.55mM ²⁰	>5.55mM	4.5–8
Sweat	Swab,tattoo	Glucose	0.06–0.11mM	0.01–1mM	4.5–7
Saliva	Swab	Glucose	0.23–0.38mM	0.55–1.77mM	6.2–7.6
Ocular Fluid	Swap,Contact lens	Glucose	0.05–0.5mM	0.5–5mM ^{21,22}	6.5–7.6
Exhaled breath	Bag,Coldtrap	Acetone	0.1–2ppm	0.1–103.7ppm	7.2–7.4

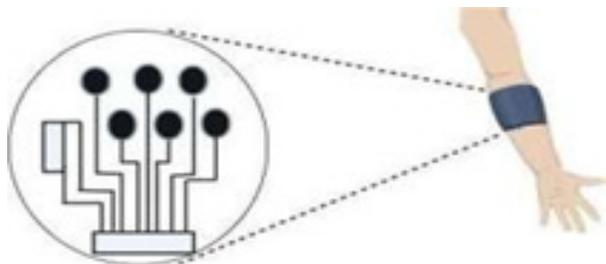


Figure 4: Sweat Based Glucose Biosensor

continuous sample secretion for accurate measurement. It is helpful in providing correct vision along with monitoring. It has many problems like generation of heat during use which causes irritation and damage to the eyes or blindness as a result protein glycation in the eye blood vessels. Unfortunately, this device also does not offer a quantitative measurement concentration of glucose in tears.²⁶

Breathe Analysis

It is an additional method of monitoring health issue. Volatile organic compounds (VOCs) are by products produced by the body's metabolic processes. These are the biomarkers that travel through the blood, cross the alveolar-thoracic contact, and leave the body through the breath. Non-invasive glucose sensors based on breath-acetone are another approach that is utilized. In general, the breakdown of fatty acids into ketones results in the production of a high-energy molecule, which is known as ketogenesis, its rate is regulated by insulin, glucagon. Diabetic ketoacidosis is caused by an increase in acetone content as a result of insulin insufficiency. In type 1 diabetes, the amount of acetone inhaled can reach up to 25 ppm and is typically between 0.2 and 1.8 ppm in diabetics and 1.25 and 2.5 ppm in healthy individuals.²⁶ It is a new detection technique that determines the blood glucose level by sensing the amount of acetone in exhaled air. There is some debate on the relationship between blood glucose levels and breath acetone concentrations reported in diverse literatures.

Interstitial Fluid

Extracellular fluid which surrounds the tissue cells has same potential as blood for diagnosis of various biomarkers. Biological analytes and smaller molecules get readily exchanged between blood and interstitial fluid simply by diffusion. As a result, it is used for minimally invasive determination of various metabolic disorders. As it overcomes the problem of Invasive monitoring and patient compliance. ISF is continuously preferred site for sensing glucose levels, as it is very easy to access and carries a low infection risk as compared to the blood stream(Figure 5).²⁷

Role of Semipermeable Membrane in Glucose Bio-sensing

There are mainly two main approaches for decreasing the working electrode potential for preventing interfering substances oxidation at electrode surface either by introducing additional substances in to either through the deposition of semipermeable membranes or the bio-selective membrane.²⁸

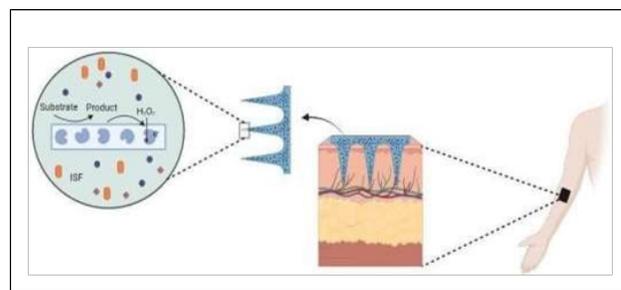


Figure 5: ISF Based Glucose Bio-sensing

These membranes are used in biosensing applications which allows preferential passage of certain analytes based on their size and charge of ions and molecules via diffusion (Figure 6). These are of biological or synthetic origin and limit the diffusion of unwanted analytes which interferes the reactions of biological recognition element (e.g., enzyme). Sensing parameter of enzyme can be improved by using mediators and semipermeable. Addition of semipermeable membrane has many advantages in increasing the selectivity and sensitivity of glucose biosensors. It helps to encapsulate the enzyme by providing a microenvironment which is conducive in enhancing the stability by preserving the enzyme viability of glucose biosensor by preventing the leeching of enzyme. The first biosensor developed by Clark consists of an oxygen electrode, an inner oxygen semipermeable membrane, a thin layer of the enzyme glucose oxidase, and an outside dialysis membrane. It measures decrease in oxygen concentration, which is directly proportional to the amount of glucose.

The bio-recognition element is first placed inside a semipermeable membrane in most glucose biosensors, and then the outer membrane coating is added to protect the inner membrane. Biocompatible semipermeable membrane use had demonstrated good operational stability and increased successful implantation of enzyme. It showed improved sensing characters like stability on long term and operational lifetime.¹⁵ Some of the Enzymatic biosensor Membranes are Cellulose acetate membrane, Nafion based membrane, chitosan- based membrane, Poly (2- hydroxyethyl Methacrylate) (pHEMA) based membrane and other polymer membranes etc.

Limitations and Cost- effectiveness of CGM²⁹⁻³¹

- Replacement of the sensor needed to be done due to performance parameters.
- The main challenges with CGM are access, reimbursement, and high prices.
- CGM was not cost-effective based on conventional metrics during the first 6 months of use, though there was considerable uncertainty surrounding these results.
- More time is consumed to train the staff using CGM.
- Discontinuing CGM within a year is due to discomfort or technical problems while using the device.
- 42% of the persons using CGM felt discomfort when wearing the sensor, 33% are having problems inserting the sensor, 30% had issues with the adhesive used, 28% had issues with proper working of sensor, 27% of people using CGM experienced too many alarms, 25% were concerned

about the accuracy of the CGM data, interference with sports was complained by 18%, and 18% reported skin reactions.

Device Size, Miniaturization and Lifetime.

Two kinds of CGM devices are available with respect to size (i) Semi-implantable device which is either micro dialysis based or transcutaneous based implant. (ii) Implantable CGM in which all sensing, powering, and wireless communication within a small device. In case of semi-implantable device, a tube is used to withdraw fluid present inside the body and sensing material is coated over its surface and is connected to a wireless device. But the main problem with this in presence of open wound latter, which further function as infection site which is not observed with implantable devices.

In response to miniaturization of an Implantable electrochemical based CGM there is need of micro and nanofabrication. The major problem in miniaturizing CGM device is powering the sensor and wireless transmission. For invasive devices the needle or the sensing component need to be small and but, in implantable CGM, the device needs to be extremely small which, need miniaturizations of all functional components like electrodes, power source, sensing elements and signal processing units etc.³²

In comparison to saliva-based sensor interstitial fluid sensor has shorter life span on average of 8 days. Currently maximum sensor lifetime of CGM is 14 days. After, that they need to change the sensor which is inconvenient and costly. Other than, that failure modes are like electrode, enzyme degradation, biofouling membrane delamination, components failure, electronics failure will all promotes shorter operation lifetime. So, improvising the enzyme stability and accuracy will have a significant effect on promotion and commercialization of device.^{32,33}

CONCLUSION

According to 2019 estimation, 463 million people are diagnosed with Diabetes. It is predicted that by 2030 579 million and 700 million people are expected to be diabetic. As half billion people are suffering from diabetes, there is a demand for development of device to deal with the situation. Most of the Glucose biosensors are available from past decades but, it is not applicable for patients with severe hypoglycemia

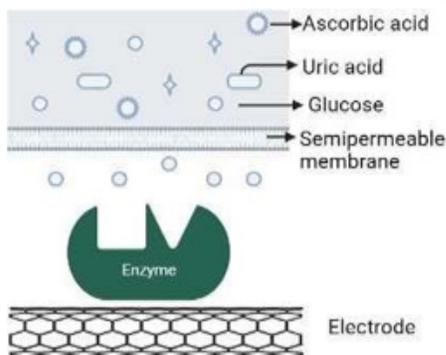


Fig 6: Semipermeable membrane for Glucose Bio-sensing

because, they need to get continuous glucose reading. To get continuous glucose reading CGM device will be helpful in doing that. CGM achieve its continuous monitoring through direct contact with interstitial fluid and the transducer through micro-dialysis technique. It has both, accuracy and precision as compared to needle-type glucose sensor.

In near future, there is a wide scope of developing a fully automated closed loop (Artificial pancreas system) technology used in diabetic care. In this there are three main components, i) CGM which continuously sends the data to ii) digital controller where, it analyzes and make the decision on hormone therapy and send the information to iii) the insulin pump to work accordingly. In comparison to other closed loop technologies the main innovative feature in it is digital controller.

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