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# Application of Continuous Glucose Monitoring for Diabetes Detection

Mingxi Pan *

College of Natural Sciences, University of Massachusetts Amherst, MA, USA

* Corresponding Author Email: mpan@umass.edu

**Abstract.** Diabetes is a serious chronic disease characterized by high blood glucose. The prevalence of diabetes is very high in the whole world. If isn't monitored and unmanaged, diabetes can lead to many severe health complications such as heart disease, stroke and kidney disease. Implantable continuous glucose monitoring (CGM) system is the current technique for monitoring the concentration of blood glucose for diabetes patients. There were two common types of implantable CGM in the market, which were electrochemical and optical. Electrochemical CGM systems were developed earlier and used in the market. Only one optical CGM system was used in the market, and many others are still in development. However, optical CGM has more benefits for diabetes patients. This research will show how electrochemical and optical work in the CGM system. It will describe the advantages of the optical CGM system, by comparing it with the electrochemical CGM systems. There are two pieces of research about testing the safety and accuracy of the optical CGM system. It would show how optical CGM systems have a high potential in the area of diabetes. Also, it will describe how optical CGM systems have a high possibility of becoming the future trend in CGM systems.

**Keywords:** diabetes; CGM system; optical.

## 1. Introduction

Diabetes is an incurable chronic illness affecting a large number of people in the world. In the past decades, the prevalence of diabetes has continued to increase. According to an International Diabetes Federation survey, about 9.3% of the adult population gets diabetes [1]. In the past, diabetes used to happen in adults. However, there are more and more cases of children who get diabetes. Diabetes is one of the big reasons leading causes of death and is associated with human blood glucose. Some tests could determine the level of blood glucose, such as the Fasting Blood Glucose Test, Oral Glucose Tolerance Test, and HbA1c. However, those tests have many disadvantages. They are not accurate since they cannot determine the blood glucose fluctuations. Any dysglycemic events will not be determined and might affect the health of the diabetes patients. Their data feedback delay might cause the diet tailored to the report to be not ideal in controlling blood glucose. These traditional tests are inconvenient since they not only require patients to empty stomachs but also require them to take samples from fingerstick blood, causing a lot of pain for the patients. Intending to change this situation, scientists proposed the concept of continuous glucose monitoring (CGM).

In the early 1990s, the first CGM system was developed [2] and the first commercialized CGM was launched by Medtronic MiniMed. CGM is an important point in the development of diabetes management technology. It allowed doctors and patients to monitor and record the dynamic changes in blood glucose levels. Wearable CGM Systems and implantable CGM systems are the two most common CGM systems today. Wearable CGM systems are usually worn on the upper arm or abdomen. It detects blood glucose by a small needle-like sensor. The advantages of the wearable CGM are providing continuous monitoring of the body's blood glucose level. It is easy to learn how to use it and reduce the pain of the frequent finger-prick blood tests. However, wearable CGM can be expensive and might cause skin problems such as allergic reactions. It is also required to replace sensors in a short period. Compared to wearable CGM, implantable CGM is a newer technology. The sensor of the implantable CGM can be used for several months, which provides long-term monitoring of the blood glucose level. It doesn't need to be maintained in a short time, and it will not affect daily activities. It also reduces skin problems due to reasons such as allergic reactions. However, it is a more expensive instrument, and it requires minor surgery. The implantation process can lead to complications. Other than wearable and implantable CGM, there are also many CGM systems that are still under development. Non-invasive CGM technologies is one of the development projects. The concept is using specific wavelengths of light to measure blood glucose levels without hurting patients. Wearable optical CGM is an improvement of wearable CGM, which uses optical instead of needle-like sensors. It will not hurt patients and it looks more like a temporary tattoo. Edible sensors have the concept of measuring blood glucose levels in the stomach. The research and development direction of the CGM systems is equipment that is painless, convenient, and quick results. As the mature of the CGM systems technology in the future, there will be more options to choose from for the patients.

The current state of CGM systems uses two types of principles, including electrochemical and optical CGM systems. Electrochemical CGM systems have three generations. Two of them have been used in the market, and the third generation is still in development. Optical CGM systems are usually more accurate. There are more advantages of optical CGM systems such as high sensitivity, less frequency in changing, less pain or possibility of infection for patients, less discomfort, fast response, and longer lifespan. However, there is only one type of optical CGM system in the market and others are still in development. Optical CGM systems are safe for patients and possibly excellent than the current CGM systems device by using electrochemicals. It is expective that optical CGM systems will become a higher accurate device in diabetes therapy. This research will analyze the detection principle of these two CGM systems and their application performance in the detection of diabetes.

## 2. Mechanism of CGM systems

CGM systems usually have three components. First, it is the main part, where is a sensor that continuously monitors the concentration of glucose. This sensor will be inserted into the fatty tissue and measure the glucose concentration in the interstitial fluid continuously. Second, it is a transmitter that transmits data from the sensor to the receiver. Third, it is a receiver like a phone or other devices [2].

### 2.1. Electrochemical CGM systems

For the electrochemical sensors, there are usually two generations of the principles using glucose oxidase (GOD or Gox) as the enzyme. For measuring the glucose concentration, usually according to the production of hydrogen peroxide by GOD and the electric current release. In the reaction, glucose, GOD, and oxidized cofactor will convert to gluconic acid, GOD, and reduced cofactor. With the combination of a reflectometry monitor and color-developing reagents, this system is considered the first generation of a personal glucose monitoring system. Compared with the first generation, the second generation is convenient and less painful. The requirement of the blood sample is less than 1 μl, which is 30 times less than the first generation. With the electrochemical principle, the second generation uses disposable electrode sensor strips. The second generation uses a mediator instead of oxygen. Mediator is used for the oxidative half-reaction in the oxidation of glucose by GOD or glucose dehydrogenases (GDHs). Several GDHs work for the glucose concentration measurement. For example, there are nicotinamide adenine dinucleotide dependent GDH, pyrroloquinoline quinone dependent GDH, and flavin adenine dinucleotide dependent GDHs. Based on the stability and substrate specificity of GOD, most of the CGM systems are equipped with electrochemical glucose sensors with GOD as the enzyme in the first and second generation. However, GDHs have the disadvantage of lack of compatibility.

Fig. 1 shows how these different generations of the sensor work. The main difference between the first and second generations is using the mediator instead of GOD. There is third-generation glucose sensing, and it is not completely developed yet. The third generation has the principle of using open circuit potential (OCP) to measure glucose concentration. It combines the DET type flavin adenine dinucleotide glucose dehydrogenase and wireless transmission system. It doesn't require oxygen or mediators as a sensor. The enzyme can transfer electrons directly to the electrode [3]. This generation has the advantage of stability for a long time running, high reproducibility of measurement, and persistence. This type of generation could be the future trend.

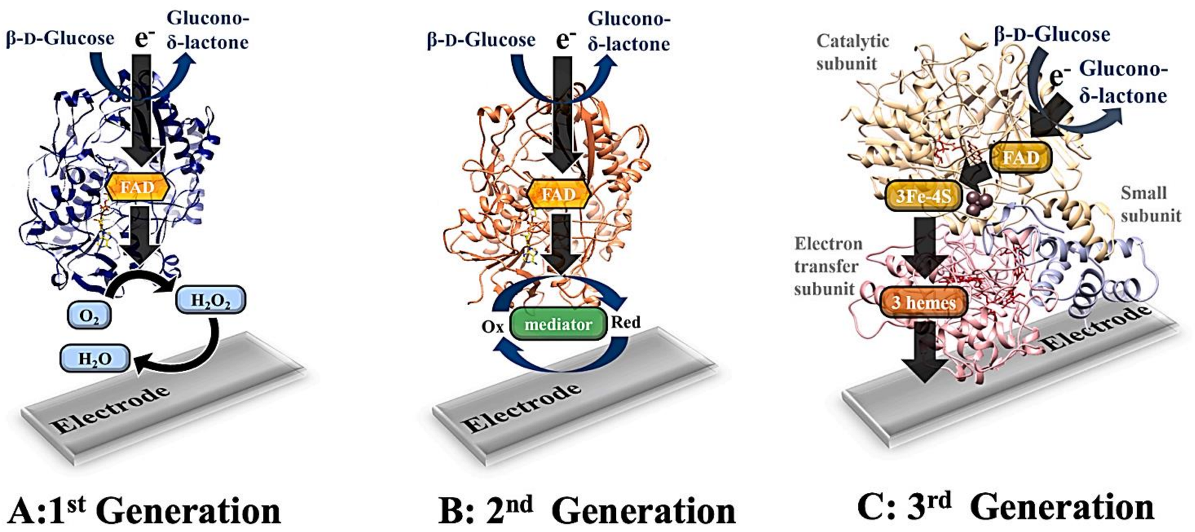


**Fig. 1** Three generations of electrochemical glucose sensing principles [3].

### 2.2. Optical CGM systems

Different from electrochemical-based glucose monitoring, optical glucose sensors were also developed into a very successful CGM system. Optical glucose sensors use glucose-binding molecules and abiotic synthetic molecules represented as diboronic acid derivatives [3]. There are several methods to measure glucose levels by optical glucose sensors. Based on the optical rotatory dispersion, substances like glucose can rotate the plane of polarized light passing through them. This rotatory power was able to calculate the concentration of glucose. Based on the infrared spectroscopy, there were specific absorption peaks for the glucose molecules. The intensity of the peaks could represent different concentrations of glucose. Fluorescence sensing technology could be used for glucose sensors. The principles of these glucose sensors were based on the properties of the fluorescent molecules. When the fluorescent molecules are exposed to light with a specific wavelength, they can absorb and produce fluorescence. When these fluorescent molecules react with different concentrations of glucose, they will respond at different intensities or spectra. By monitoring the changes in the fluorescent molecules, sensors could measure the concentration of glucose.

## 3. Application

In today's market, there are two types of CGM, which are electrochemical and optical. Electrochemical CGM has been more commonly used since it was developed earlier and many optical CGM systems are still in the process of development. However, most electrochemical CGMs have the disadvantages of not being suitable for personal care, too large sensor volume, too high costs for home monitoring, and decreased accuracy caused by signal drift [4]. Electrochemical CGM requires patients to replace the sensor every 7 to 14 days. These might increase the cost of maintenance and some skin problems such as infection. Since the replacement period is short, it is also inconvenient for patients. Electrochemical CGM had a delayed reading problem. This means there might be a high error between the actual glucose level and the reading on the device. Besides those, electrochemical CGM requires periodic calibration by using the traditional glucometer. It is not only inconvenient but also has a possibility of improper operation.

Eversense is an implantable CGM system that first uses an optical sensor. It applied the principle of fluorescence sensing technology. This is a commercial CGM system that has been accepted and used by a large number of patients in different countries. There were several different types of sensors, and the lifespan of these sensors could last for 90 days or 180 days. It is considered as a very long longevity in the CGM system. Before Eversense, most of the CGM systems were used by electrochemical sensors. Therefore, the launch of Eversense represents a big step forward for the CGM system. This optical sensor changes many current problems such as requiring frequent replacement and being painful for the patients. To ensure this is a reliable, convenient, and safe glucose monitoring technology, scientists did a lot of research, including many clinical experiments.

Eversense CGM system had research about safety for type 1 diabetes and type 2 diabetes. Patients use implantable CGM systems. To update patients' body status, there is a Post-Market Clinical Follow-up registry which records and evaluates this Eversense CGM system. Every adverse event will be recorded, and the primary safety point will be determined based on the serious adverse events. Post-market clinical Follow-up registry recorded 3023 patients in European countries and South Africa from June 2016 to August 2018. For the summary of the safety results, 133 adverse events were reported and 117 of them were considered as related, due to several reasons such as procedure, device, drug, and others. The most common reason reported for adverse events was infection and the problem could be solved by removing the sensor. The percentage of patients who have infractions is 0.96%, which is lower than 7.3%-11.5% for the insulin infusion. 23 cases failed to remove the sensor the first time, but sensors were removed successfully the second time in 20 of them. There are no reports of any adverse effects for the patients who fail the sensor removal the first time. There were not any cases of serious adverse effects, and it reached the safety level. Based on the percentage, adverse effects relative to the Eversense CGM system are really low and it shows this CGM system is safe during the clinical experiments. Also, in the overall summary from the report of the Pos-market clinical Follow-up, the safety level is consistent over multiple periods in patients with type 1 diabetes and type 2 diabetes. For sensor longevity, the sensor survival through intended sensor life was 91% for the 90-day sensor and 75% for the 180-day sensor [5].

There was another research on the Eversense CGM system with 181 patients at 8 USA sites. Patients had either type 1 diabetes or type 2 diabetes for more than 1 year and must be over 18. During the research, 96 patients inserted two sensors. In these secondary sensors, 53 sensors were identical to primary sensors for analysis of precision and 43 sensors were sacrificial boronic acid sensors. Those secondary sensors were used to utilize a glucose calculation algorithm and determine the sensitivity of any changes. Study visits on days 1, 7 or 14, 22, 30, 60, 90, 120, 150, and 180. The time of sampling is up to 10 hours. Female patients also conducted urine pregnancy testing. Any adverse events and serious adverse events will be recorded and evaluated. Patients were required to calibrate twice per day during the study. Any overdue will be subject to corresponding measures. After the visit on day 180, the sensor will be removed, and 8 patients have a follow-up after 10 days to evaluate the healing of the removal site. As a result, 170 patients completed the 180-day research. there are 49613 matched glucose pairs collected in this research. To evaluate the accuracy of the Eversense CGM system, data was measured and collected by the Yellow Springs Instrument (YSI). For the overall mean percent, 15%/15% of the YSI values had 85.6% of CGM readings within it. And for the 20%/20% of the YSI values, there were 92.9% of the CGM reading within it. This showed how accuracy of the data by the primary CGM sensor. In other results, the confirmed rate of detection of hypoglycemia and hyperglycemia was 93%-99%. For the primary sensor and its identical match, the precision measure was 10.1%. This result is better than other commercial CGM systems in the accuracy measurement. The result of the sacrificial boronic acid sensors had similar results compared to the primary sensors. There were no unanticipated adverse events and no related serious adverse events in the overall research. This provides evidence that the Eversense 180 CGM system is safe. Eversense CGM system has the advantages of safety, lasting, portable, precise, and could alarm in any sudden situation, Eversense CGM system will have a very good future trend in medicine [6].

Although optical sensors are facing a lot of challenges, the outstanding advantages still provide great opportunities to improve CGM systems. Optical sensors can more accurately measure the concentration of glucose since it does not consume local glucose molecules. Optical sensors usually have three times longer lifespan than the electrochemical sensor. Based on that, patients will reduce the pain, discomfort, and risk of any diseases. With the development of the technology of optical sensors, it is possible to achieve a painless CGM system. Although other types of optical sensors, such as hydrogel sensing and optical glucose sensing, also have very high sensitivity and fast response time, fluorescence sensing is still the only optical sensor that is applicable in the market. However, fluorescence sensing has the disadvantage of loss through the photobleaching process. It still needs to be further researched and improved to raise the lifespan of the sensor. But overall, the advantage of the optical sensors was showing high potential in CGM systems. After the development of some data processing methods, it is possible to achieve a higher accuracy technique on glucose level monitoring [4].

## 4. Conclusion

Optical CGM systems are safe and accurate based on two different groups of people's research. This is evidence that optical CGM systems can be used for patients with diabetes. Optical CGM systems show a lot of advantages, which are safety, high sensitivity, less frequency in changing, less pain or possibility of infection for patients, less discomfort, fast response, and longer lifespan. Compared with most of the CGM systems in the market, which used the theory of electrochemical, optical CGM systems show more unique advantages in diabetes and high potential in the future of CGM systems. After the development and clinical experiments, when more optical CGM systems are launched, patients will have more options to choose from for blood glucose monitoring. At the same time, diabetes will have more options to be monitored and managed.

## References


[1] Malik J, Kim S, Seo J M, et al. Minimally invasive implant type electromagnetic biosensor for continuous glucose monitoring system: In vivo evaluation. IEEE Transactions on Biomedical Engineering, 2022, 70(3): 1000-1011.

[2] Freckmann G. Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. Journal of Laboratory Medicine, 2020, 44(2): 71-79.

[3] Lee I, Probst D, Klonoff D, et al. Continuous glucose monitoring systems-Current status and future perspectives of the flagship technologies in biosensor research. Biosensors and Bioelectronics, 2021, 181: 113054.

[4] Ahmed I, Jiang N, Shao X, et al. Recent advances in optical sensors for continuous glucose monitoring. Sensors & Diagnostics, 2022, 1(6): 1098-1125.

[5] Deiss D, Irace C, Carlson G, et al. Real-world safety of an implantable continuous glucose sensor over multiple cycles of use: a post-market registry study. Diabetes Technology & Therapeutics, 2020, 22(1): 48-52.

[6] Garg S K, Liljenquist D, Bode B, et al. Evaluation of accuracy and safety of the next-generation up to 180-day long-term implantable eversense continuous glucose monitoring system: the PROMISE study. Diabetes Technology & Therapeutics, 2022, 24(2): 84-92.