Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2024, 15, 503-510
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

A Review: Biosensor Progression in Glucose Monitoring for Patients with Diabetes

Megan Sweeney

Electrical Engineering Department at the University of Massachusetts Lowell, Lowell, MA, USA
Email: megan_sweeney1@student.uml.edu

How to cite this paper: Sweeney, M. (2024) A Review: Biosensor Progression in Glucose Monitoring for Patients with Diabetes. *Advances in Bioscience and Biotechnology*, **15**, 503-510.
https://doi.org/10.4236/abb.2024.158031

Received: July 19, 2024
Accepted: August 27, 2024
Published: August 30, 2024

Abstract

Diabetes is a condition that can come to the surface at any point throughout a person's life. Although Type 1 and Type 2 Diabetes have different triggers that cause them to arise, a person can experience similar complications from either if not monitored and treated accordingly. Through the Diabetes Control and Complications Trial, it was found that a significant way to monitor diabetes is through glucose levels in a person's body. The research surrounding glucose monitoring dates to the mid-1800s, with the first successful reagent for glucose testing being developed in 1908. Since then, glucose sensing has become one of the most rapidly growing areas of research and development in biosensor technology, creating a competitive market for more advanced, accurate, and convenient glucose monitoring. This article reviews the history of biosensors used for glucose monitoring, and major advancements in biosensor technology to enhance performance and improve quality of life for patients with diabetes.

Keywords

Biosensor, Continuous Glucose Monitor, SMBG, Advances in Glucose Monitoring, Diabetes

1. Introduction

1.1. Diabetes

Diabetes is an autoimmune disease that makes it difficult for people to control their glucose levels. This is caused when a person's pancreas is unable to produce, or properly use, insulin. There are three forms of diabetes: Type 1, Type 2, and gestational. Gestational diabetes occurs when there is an elevated level of glucose during pregnancy. Diabetes can arise at any time in a person's life. Improper or lack of treatment for patients with diabetes can result in severe complications related to microvascular and macrovascular complications. Microvascular complications include those that affect small blood vessels, such as retinopathy, nephropathy, and neuropathy. Macrovascular complications are those that affect large blood vessels and can include coronary artery disease, high blood pressure, and kidney disease. These complications have long-term effects on the body and are a major cause of blindness, kidney failure, heart attacks, strokes, and lower limb amputation [1]-[4].

The number of people diagnosed with diabetes is constantly rising. From 1980 to 2014 the number of people diagnosed with diabetes quadrupled from 108 million to 422 million. In 2019, diabetes and complications with diabetes caused 1.5 million deaths. These rising numbers make it important to continue to develop easier and less invasive ways of monitoring glucose. Biosensors and their continued evolution play a key role in this [3] [5].

1.2. Biosensors

There are several parts that make up a biosensor: the analyte, the bio-recognition element, the transducer, signal processing component, and display of results. The analyte is the target substance to be detected. For the purposes of this paper, the analyte is glucose, but it can be any specific substance in a sample. The bio-recognition element recognizes the analyte by using enzymes, antibodies, cells, etc. to distinguish the target analyte from the other contents in the sample. Transducers receive the biological component from the bio-recognition element and convert the biological input into a measurable signal. That signal is then transmitted to the signal processing component where the signal is amplified, interpreted, and converted to a form that is human readable and the results are displayed for the user. These results can be represented in a quantitative or a qualitative way, for instance, glucose levels might be determined using a specific number, while a COVID-19 test result will be determined by a Positive or Negative result [6]-[10].

There are multiple domains where biosensors are utilized, including industry, medicine, military, and domestic. However, the most commercially successful and very rapidly growing industry of biosensors are glucose biosensors [7] [8].

The accuracy and precision of glucose biosensors are detrimental to monitoring glucose for patients with diabetes. With each new glucose monitoring device, these metrics improved but were still influenced by several factors. These include environmental conditions, such as temperature and humidity, the patient and quality of the glucose sample, calibration procedures, and sensitivity, reproducibility and lifetime of the sensor.

2. Biosensors in Glucose Monitoring: A History

2.1. Dipstick Using Urine Samples

The first efforts in quantifying glucose started in the mid-1800s and were attempted using urine samples. However, it wasn't until 1908 that the first reagent for glucose testing in urine was developed by Benedict. This discovery laid the original foundation for modern diabetes care. In the mid-1900s, Clinitest, also referred to as the Dipstick, was developed for glucose testing and functioned by associating the color of the heated solution to a proportional amount of glycosuria when glucose was oxidized [11].

Since urine samples typically use a color scale to quantify a range instead of a specific value, it's often used for qualitative detection, where accurate results aren't as important. This means these biosensors have low sensitivity and detecting glucose in urine is usually a sign of severe Diabetes, therefore, they are most often used to diagnose Diabetes. The Dipstick tests are also single use and cannot be reused for another test. Reusability of a biosensor is important as it reduces the cost per test and allows for continuous calibration resulting in higher accuracy in results. There has been development of these types of biosensors to improve the sensitivity and accuracy of measuring glucose in urine such as the graphene field-effect transistor (GFET), which increases quantification ability and reproducibility. Using the Dipstick with urine samples is a simple, low cost, non-invasive, and pain-free way to test the health of a patient, however, there are still many setbacks to these biosensors including influence from temperature, pH, and humidity [12].

2.2. Blood Glucose Strips

The research and development of quantifying glucose continued in the mid to late 1900s. Researchers started turning to blood samples to test glucose levels and quickly realized using blood gave more accurate results. In 1963, Dextrostix was created by Ernie Adams, which uses a paper strip that changes color when a blood sample is applied. The intensity of the color on the strip indicates the concentration of glucose in the blood sample and is read by visually comparing the color of the strip to a color concentration chart. Not long after, in 1970, Anton H. Clemens invented the first blood glucose meter and self-monitoring system called the Ames Reflectance Meter (ARM). The ARM detects the color concentration on a Dextrostix and quantifies the glucose level on an analog display on the ARM. The ARM was originally only intended for in-office doctor use; however, Richard K. Bernstein was the first patient to test his blood glucose with ARM and pushed for self-monitoring blood glucose (SMBG). The precision and accuracy of these devices were poor, but the push from Bernstein to exercise the idea of SMBG motivated research and development to improve these devices and make them more independently available to patients [11] [13].

The Dextrometer was launched in 1980 and used Dextrostix with a digital display. Throughout the rest of the 1980s, more glucose strips and meters were created and SMBG became a standard care for patients with Type 1 diabetes. The advances in this technology, paralleled with A1C testing and insulin therapy, sprouted the Diabetes Control and Complications Trial. This trial ended the debate about the relationship between glucose control and diabetes complications [11].

The Diabetes Control and Complications Trial spurred improvements in sensor sensitivity, new detection techniques, and smaller component development in the 1990s [9]. This drive continued into the early 2000s with the development of nanotechnology and microfabrication techniques. Due to the focus on miniaturization during this period, biosensors were created with higher sensitivity. Also, when electrochemical test strips were created, SMBG technology improved in such a way that smaller amounts of blood were required for testing. With the advances in lancets, new enzymatic tests, better test strips, and smaller amounts of blood, SMBG was less invasive and less painful than it ever had been at this time. Not only that, but these advances improved the accuracy, ease of use, reliability, and speed of results from blood glucose test strips and meters [11] [14].

Today, blood glucose strips require a small amount of blood, provide rapid results, have high accuracy and reliability, and are compatible with various glucose meters. Some blood glucose strips can also integrate with Continuous Glucose Monitoring (CGM) systems (CGMs are discussed in the next section). Having access to easy-to-use technology for regularly monitoring blood glucose levels helps patients make informed decisions about their diet, exercise, medication, and respond quickly to episodes of high or low blood sugar. As a result, this reduces a patient's risk of severe diabetes-related complications [15].

Even with the current advancements, finger pricking and test strips are still single use, can be painful, invasive, and expensive especially if a patient needs to check their blood glucose levels numerous times throughout the day. They also have short expirations dates, and are easily affected by temperature, humidity, and the quality of the blood sample. These can cause variation in the accuracy and reliability of the test results when using blood glucose strips [9] [16].

2.3. Continuous Glucose Monitoring (CGM)

As the number of people with diabetes increased, so did the demand for a more practical, accurate, and convenient way of monitoring glucose levels. There had also been some research done that hinted at the value of a patient tracking their levels continuously throughout the day. The high demand and increased research and development resulted in another major advancement in biosensor technology for glucose monitoring called Continuous Glucose Monitoring (CGM), which allows a patient to check their glucose levels in real time. This idea, along with implantable glucose sensors, dates back over 40 years ago but didn't come to fruition until 1999 and early 2000 when the first implantable glucose sensors were released [17] [18].

CGM and implantable glucose sensors sprouted in 1999 when Minimed was announced as a replacement for traditional blood glucose monitoring. This was the first CGM that recorded glucose levels over a three-day period and required sensor calibration with a finger prick every 6-12 hours. The data from the sensor also wasn't available to the patient right away and instead required a health provider to download and analyze the data. This was tedious for both the patient and the health provider and over the next decade several new advances in CGM evolved [17] [18].

In 2004, Guardian introduced wireless transmitting from the sensor to a receiver to read the blood glucose levels and signaled an alert to the patient for high or low glucose levels based on the allowable range programmed into the receiver. By 2006, Medtronic Gardian RT and Dexcom STS were released, which allowed patients to see their glucose levels in real time for up to three days. The lifespan of CGM was extended in 2007 when Dexcom STS-7 came out, which extended the lifespan to seven days, allowing patients to see their glucose levels over a seven-day period [17] [18].

A new feature ignited in 2015 when Dexcom Share and MiniMed Connect secondary receivers came out. These devices made CGM compatible with mobile devices through their respective company-released apps to enable patients to view their glucose levels on their phones. However, the need to carry a separate receiver wasn't eliminated until Dexcom released the G5 later that year. The next year, in 2016, Senseonics created Eversense that became the only implantable CGM with a lifespan of 90-days. This device was surpassed by Eversense XL in 2017 that had a lifespan of 180 days; this is 6 months of continuous monitoring. This was a huge leap in the matter of a couple years and the longest lasting CGM there is currently in the world. There have been new releases of 6-month implantable sensors, like the Eversense E3 that was released in 2022, but nothing lasting longer than 6 months [17] [18].

Another key feature was developed in 2018 that allowed patients to view their current glucose levels as well as their glucose trends. This feature was included in the FreeStyle Libre, which was an implanted sensor that consisted of a lifespan of 14 days and extinguished the need for finger prick calibrations. 2018 was also the year the FDA approved integration of the CGM Dexcom G6 with automated insulin dosing (AID) devices. AID acts as an artificial pancreas that the patient can wear on the outside of their skin, similar to a CGM. It controls blood glucose in the body and is made up of a CGM, insulin pump, and software program. After the CGM sends glucose level data to a smart phone or insulin pump, the software calculates the amount of insulin the patient's body needs and the AID injects the correct amount into the body when sugar levels rise. The combination of CGM and AID is probably the closest thing to replacing a pancreas altogether [16]-[19].

A main source of inspiration for less invasive sensors was research around how mosquitos draw blood from other living things. The anatomy of a mosquito was studied to help develop hypodermic needles and supporting mechanisms to mimic the labium of a mosquito. The CGMs discussed in this section and their progress to be less invasive can be attributed to this research [18] [20].

These high-tech, water-resistant, disposable sensors are an expensive investment, however, for a patient that requires checking their glucose levels frequently throughout the day it quickly becomes the more cost-effective and convenient method. Patients have many options of CGMs to choose from based on their needs and can choose sensors with varied lifespans and capabilities [16] [18].

3. Conclusion: Current Challenges and Future of Biosensors in Diabetes

3.1. Current Challenges

Even though technology in SMBG and CGM has progressed, there are still many challenges that linger around these devices. These include challenges surrounding affordability and accessibility, especially for uninsured patients and low-income areas. The current industry also focuses on a "one size fits all" method, but as companies advance their technology the focus should reflect on the limitations of their different market groups. For instance, the major market groups that are not being fully accounted for include senior citizens, children, and low-income families. This means future iterations of these devices should be sized to the user, easy to use, and affordable to purchase [15] [19].

3.2. Future of Biosensors in Diabetes

There is a strong need to improve invasiveness, precision, repeatability, wearability, and accessibility to patients. Less invasive ways of testing glucose are being developed, which include using optical sensors, saliva, sweat or tear fluid that can be calibrated and used. Some ideas, like contact lenses or mouthguards are being investigated as an alternative to the current wearable CGMs that puncture the skin to collect blood for measuring glucose levels. Another major development is to create more accurate and predictive glucose monitoring systems using artificial intelligence (AI) and machine learning (ML). This would further the improvement of precision and repeatability in these sensors. Other things to consider are the sustainability and environmental impact these sensors have when patients are done using them. There are investigations around using recyclable materials and packaging, biodegradable components, and finding ways to reduce manufacturing waste [15] [21].

The progress that has been made in glucose monitoring over the past century is overwhelming and has undoubtedly improved the quality of life for patients with diabetes. However, there is still much to improve on in so many different aspects of the current technology, including performance, customization, cost, accessibility, invasiveness, usability, and sustainability. With the increasing demand for these devices and high interest in research and development in this domain, the devices and technology for monitoring glucose are going to improve exponentially over the next century.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Osborn, C.O.K. (2022, July 17) Type 1 and Type 2 Diabetes: What's the Difference? 2024 Healthline Media LLC. https://www.healthline.com/health/difference-between-type-1-and-type-2-diabetes

[2] Catargi, B. and Lang, J. (2014) Biosensors in Diabetes. https://www.embs.org/pulse/articles/biosensors-diabetes/

[3] World Health Organization (2023, April 5) Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes

[4] Alakhrass, H. and Alenazi, W. (2019) Diabetes and Technology: Continuous Glucose Monitoring among Pregnant Women in Real Time. *Health*, **11**, 855-861. https://doi.org/10.4236/health.2019.117068

[5] Yoo, E. and Lee, S. (2010) Glucose Biosensors: An Overview of Use in Clinical Practice. *Sensors*, **10**, 4558-4576. https://doi.org/10.3390/s100504558

[6] Bhalla, N., Jolly, P., Formisano, N. and Estrela, P. (2016) Introduction to Biosensors. *Essays in Biochemistry*, **60**, 1-8. https://doi.org/10.1042/ebc20150001

[7] Naik, V., Sundari, T., Lalitha, K. and Lakshmi, K. (2017) An Overview on Biosensors. *International Journal of Pharmaceutical, Chemical and Biological Sciences*, **7**, 293-302. https://www.ijpcbs.com/articles/an-overview-on-biosensors.pdf

[8] Birch, B. (2018) Introduction to Biosensors. LIRANS University of Luton. https://pdfs.semanticscholar.org/c2e8/b4104a1ee7299ffde12fdadc0829d0a96f3c.pdf

[9] Ginty, J. (2024) Glucose Sensors: What They Are & How They Work. AgaMatrix. https://agamatrix.com/blog/glucose-sensors/

[10] Mehrotra, P. (2016) Biosensors and Their Applications—A Review. *Journal of Oral Biology and Craniofacial Research*, **6**, 153-159. https://doi.org/10.1016/j.jobcr.2015.12.002

[11] Hirsch, I., Battelino, T., Peters, A., Chamberlain, J., Aleppo, G. and Bergenstal, R. (2018) Role of Continuous Glucose Monitoring in Diabetes Treatment. American Diabetes Association.

[12] Hwang, C., Lee, W., Kim, S.D., Park, S. and Kim, J.H. (2022) Recent Advances in Biosensor Technologies for Point-of-Care Urinalysis. *Biosensors*, **12**, Article No. 1020. https://doi.org/10.3390/bios12111020

[13] Tonyushkina, K. and Nichols, J.H. (2009) Glucose Meters: A Review of Technical Challenges to Obtaining Accurate Results. *Journal of Diabetes Science and Technology*, **3**, 971-980. https://doi.org/10.1177/193229680900300446

[14] Lau, E. (2024, February 23) History & Types of Biosensors. https://medium.com/@emory99lau99/history-types-of-biosensors-960f5a3b2f51

[15] Diabetic Trust: The Evolution of Diabetic Test Strips from Inception to Modern Day. https://www.streetinsider.com/Globe+PR+Wire/Diabetic+Trust%3A+The+Evolution+of+Diabetic+Test+Strips+from+Inception+to+Modern+Day/23231234.html

[16] Mathew, T.K., Zubair, M. and Tadi, P. (2023) Blood Glucose Monitoring. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK555976/

[17] Wolters, C. (2022) FDA Approves Longest Lasting Continuous Glucose Monitor for Diabetes. https://www.verywellhealth.com/fda-approves-longest-lasting-continuous-glucose-monitor-eversense-5219519

[18] Continuous Glucose Monitoring. https://www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes/continuous-glucose-monitoring#:~:text=CGM%20sensors%20estimate%20the%20glucose,the%20CGM%20is%20a%20transmitter

[19] Didyuk, O., Econom, N., Guardia, A., Livingston, K. and Klueh, U. (2020) Continuous Glucose Monitoring Devices: Past, Present, and Future Focus on the History and Evolution of Technological Innovation. *Journal of Diabetes Science and Technology*, **15**, 676-683. https://doi.org/10.1177/1932296819899394

[20] Wang, G. and Mintchev, M.P. (2013) Development of Wearable Semi-Invasive Blood Sampling Devices for Continuous Glucose Monitoring: A Survey. *Engineering*, **5**, 42-46. https://doi.org/10.4236/eng.2013.55b009

[21] Johnston, L., Wang, G., Hu, K., Qian, C. and Liu, G. (2021) Advances in Biosensors for Continuous Glucose Monitoring towards Wearables. *Frontiers in Bioengineering and Biotechnology*, **9**, Article ID: 733810. https://doi.org/10.3389/fbioe.2021.733810