Vol. 4 No. 3 (2025)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Advances in Glucose Biosensors: Implications for Clinical Applications

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Received on 16 July, 2024

Accepted on 15 Aug 2025

Published on 16 Aug 2025

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Abstract

Glucose biosensors have proven to be invaluable in managing diabetes by monitoring blood glucose levels. Significant improvements in glucose biosensor technology during the previous 50 years have led to the invention of a variety of devices, including point-of-care devices, continuous glucose monitoring systems, and noninvasive glucose monitoring systems. Despite these advancements, obtaining accurate and trustworthy measurements of blood glucose still presents difficulties. The necessity for additional technological improvements in glucose biosensors, standardization of measurement objectives for their effectiveness, and ongoing user guidance and instruction are some of these difficulties. The history,

underlying ideas, analytical capabilities, and present status of glucose biosensors in clinical applications are all briefly discussed in this review article.

INTRODUCTION

Diabetes mellitus, a common endocrine condition that affects glucose metabolism, is a major health concern on a global scale. It is a major contributor to morbidity and death, especially in advanced cultures. Diabetes is becoming more common; it affected approximately 9.6% (20.4 million) of US adults between 2003 and 2006 [1]. By the year 2050, it is anticipated that the number of Americans with diabetes would increase to 48.3 million [2]. According to predictions from the World Health Organisation (WHO), By 2030, there might be a staggering 368 million individuals with diabetes globally, compared to an estimate of 171 million individuals in year 2000 [3]. A recent study projected that in 2010, the global occurrence of sugar between adults between 21 to 78 age was 6.5%, affecting around 286 million people. It is anticipated that by 2030, it would increase to 7.7%, impacting over 439 million individuals. An inactive lifestyles, altered eating patterns, and the increasing prevalence of being overweight are believed to be the primary drivers of these growing rates.

Numerous diagnostic procedures are used to identify and treat diabetic patients. The measurement of HbA1c, that also helps with patient monitoring, and the levels of glucose in the circulatory system serve as the main diagnostic indicators for diabetes. Many research investigations [6–12] have shown that monitoring their own of blood sugar levels (SMBG) is a crucial tool in the care and treatment of diabetes. Individuals suffering from diabetes ought to perform self-monitoring of blood sugar levels (SMBG) for the purpose to prevent or postpone the onset of microvascular disorders (retinopathy, kidney failure, and neurotoxicity) and macrovascular issues (heart stroke

and cardiovascular disease). Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that strict management of elevated glucose levels reduces the possibility and severity of severe coronary artery disease and also delays the onset of adverse effects like kidney disease, damage to the nervous system, and degenerative retinal degeneration among individuals with diabetes. Regular tracking of blood glucose can help to detect hypoglycemia and provide real-time assistance for modifying medicines, diets, and exercise regimens to meet glycemic objectives. Frequent blood glucose monitoring might provide helpful information for improving and even modifying patient therapy regimens.

The ADA advises SMBG for patients receiving extensive insulin therapy (minimum three times per day), although it may also be beneficial for individuals receiving less frequent administration of insulin, non-insulin medications, or just medical nutrition therapy [16].

The suggestions to keep blood sugar concentrations in the normal range have prompted the development of adequate glucose-measuring instruments. Rapid advancements in biosensor technology have made them an effective analytical tool, particularly in the field of medicine. The biosensor market is now dominated by glucose biosensors. Around 85 percent of the biosensor marketplace, which was worth $5.1 billion USD in 2005 [17], was made up of glucose biosensors. The market for glucose biosensors is expanding quickly, and producers are engaged in fierce rivalry. In a recent analysis, Global Industry Analysts, Inc. predicted that by 2012, the international market for biosensors that detect glucose and sugar test strips will be worth $12.6 billion USD.

This article provides a broad overview of the evolution of biological sensors, as well as their working principles, benchmarks of performance, and current state of sugar biosensors. Additionally, it examines how testing accuracy is assessed in clinical practical application.

BASIC PRINCIPLES OF GLUCOSE BIOSENSORS

A biological sensor is a tiny analytical tool which incorporates a physiochemical transducer and a biologically based recognition element. It has three essential parts: (i) biological detection components that can recognise target molecules among a variety of chemicals; (ii) a device known as a transducer that can transform the biorecognition occurrence into a detectable signal; and (iii) a signal processing mechanism that can transform the signal into a format that can be read. Receptors, antibodies, digestive enzymes, DNA, RNA, bacteria, and lectins are examples of molecular identification components [22,23]. Electrochemical, visual, thermometric, electrically charged, and magnetic transducers are the primary transducer classes [24]. Due to their higher sensitivity, repeatability, ease of maintenance, and cost, biosensors with electrochemical activity are the most used for detecting glucose. Potentiometric, amperometric, and conductometric electrochemical sensors are the three main types [25–27]. Enzymatic amperometric sugar biosensors are among these and have been the subject of substantial study and usage. Amperometric sensors can be used to either directly or indirectly measure currents that come from the movement of electrons between an organism and an electrode [28,29].

The 3 enzymes that are most usually employed to measure sugar levels are glucose oxidase (GOx), glucose-1-dehydrogenase (GDH) and hexokinase [30,31]. Hexokinase is the standard spectrophotometric method used in healthcare laboratory

conditions to measure glucose [32]. The glucose biological sensors utilised in self-monitoring blood glucose (SMBG) monitors usually contain the enzymes GOx and GDH. These enzymes have various oxidative potentials, cofactors, rates of turnover, and sugar sensitivity[33]. GOx, the enzyme of choice for biosensors, is more selective for sugar. In comparison to other enzymes, GOx is easily accessible, affordable, and more resistant to extremes in temperature, ionic strength, and pH. For lay biosensor users, this permits less stringent production standards and laxer storage specifications [33–34].

The glucose biosensor works by immobilising GOx, which uses molecular oxygen to catalyse the oxidation of -D-glucose. Hydrogen peroxide and gluconic acid are produced during this procedure. Flavin adenine dinucleotide (FAD), a redox cofactor that first takes electrons before being reduced to FADH2, is necessary for GOx to work as a catalyst.

$$\text{Glucose} + \text{GOx} - \text{FAD}^{+} \rightarrow \text{Glucolactone} + \text{GOx} - \text{FADH}_2$$

The cofactor is restored by reacting with oxygen, resulting in the creation of hydrogen peroxides.

$$\text{GOx} - \text{FADH}_2 + \text{O}_2 \rightarrow \text{GOx} - \text{FAD} + \text{H}_2\text{O}_2$$

An anode made of catalytic platinum (Pt) oxidises hydrogen peroxide. Electrode shifts are easily detected and directly inversely correlated with blood glucose levels [36].

$$\text{H}_2\text{O}_2 \rightarrow 2\text{H}^{+} + \text{O}_2 + 2\text{e}$$

3 primary techniques are used in electrochemical glucose detection: assessment of oxygen consumption, estimation of peroxide concentration from enzyme activity, and use of a diffusible or immobilised mediators for electron exchange between GOx and the electrode's surface. GDH-based amperometric biosensors have grown in both diversity and number recently. GDH is made up of two different molecules: GDH-PQQ

[37–39] and GDH-NAD [40–42]. The enzymatic process is oxygen-independent. For the quinoprotein GDH recognition element, PQQ acts as a cofactor.

Glucose + PQQ(ox) → gluconolactone + PQQ(red)

The extremely effective enzyme system GDH-PQQ runs without the use of oxygen or NAD+. Although its electron transport rate is quick, it is also rather expensive [17]. NAD participates in GDH processes as a cofactor, accepting electrons and hydrogen ions that result from glucose oxidation. The reduced form of NAD produced by this process is called NADH, and it may be electrochemically oxidised.

Glucose + NAD^+ → gluconolactone + NADH

NADH → $NAD^+ + H^+ + 2e$

HISTORICAL PERSPECTIVES OF GLUCOSE BIOSENSORS

Although there are many different glucose sensors available, the basic idea behind the glucose biosensor has essentially kept constant for several decades (Table 1). The Ames Reflectance Metre (ARM), the first blood glucose metre created by Miles Laboratories in Elkhart, Indiana, was not a biosensor. It used the Dextrostix, which debuted in 1971, and a reflectometer. The first blood sugar strip, Dextrophix, was introduced in 1966 which used colour changes [43–46]. After sixty seconds, the strip was washed and put into the metre. The Ames Eyetone glucose tester was replaced in spite of being expensive and bulky. The reflectometer was used in the earliest glucose measurement instruments.

FIRST-GENERATION OF GLUCOSE BIOSENSORS

The paediatric hospital of Cincinnati's Clark and Lyons presented the initial suggestion for a biological sensor to measure sugar in 1962 [19]. A very thin covering of GOx enzyme, an oxygen electrode, an inner semipermeable membrane that allows oxygen, and an outside dialysis membrane made up this biosensor. An enzyme electrode might

be made by immobilising enzymes in an electrochemical detector. By immobilising and stabilising GOx, Updike and Hicks were able to simplify the electrochemical glucose experiment and demonstrate that the drop in oxygen concentration was precisely proportionate to the glucose level [20,47]. They were able to quantify the amount of glucose in bodily fluids by immobilising GOx in a polyacrylamide gel on an oxygen electrode[20].

The YSI analyzer (Model 23A), manufactured by the Yellow Springs Instrument Company in 1975, was the first glucose biosensor to be successful on the market. It used hydrogen peroxide amperometric detection and Clark's technique. Despite its success in laboratory applications, its wider application was constrained by the expensive platinum electrode it used.

In the beginning, glucose biosensors used atmospheric oxygen as a substrate and picked up the hydrogen peroxide that resulted. As peroxide measurements are necessary, this method is straightforward, especially for small devices [48]. The fundamental issue with 1st generation sugar biosensors was the need for a high operational voltage for the device to provide superior accuracy in the amperometric determination of H_2O_2.

The impact of naturally produced electroactive chemicals including ascorbic acid, uric acid, and certain pharmaceuticals received a lot of attention in the late 1980s. The solubility of oxygen in the body fluids was also restricted, causing oscillations in oxygen tension which is also known as the "oxygen deficit" [49].

SECOND-GENERATION OF GLUCOSE BIOSENSORS

The defects in the1st generation sensors was fixed by the second-generation sugar sensors, also referred to as mediated glucose biosensors. Redox facilitators, that are

non-physiological electron accepting molecules, were used in place of oxygen in these sensors. Significant advancements were made as as a consequence of the mediators' facilitation of the electron transport from the enzyme itself to the outer layer of the operational electrode [49]. A reduced mediator is produced and then reoxidized at the electrode instead of utilising hydrogen peroxide. Through this procedure, the mediator is returned to its oxidised condition and an amperometric signal is produced [28]. To improve the sensor's effectiveness, a number of electron mediators have been utilised [50–53]. Ferrocenes have favourable properties that make them effective mediators, such as their inertness to oxygen, stability in both oxidised and reduced forms, pH independence, bidirectional electron transfer dynamics, and rapid enzyme kinetics [53]. As intermediaries between glucose oxidase (GOx) and glucose dehydrogenase-pyrroloquinoline quinone (GDH-PQQ) enzymes and electrodes, they have received substantial research [50, 54–56]. The first investigation into amperometric blood sugar determination utilising a reactive couple-mediated, GOx-catalyzed procedure culminated in 1970 [57]. This research experiment nevertheless failed to result in widespread acceptance of amperometry for SMBG in residential settings [58].

Development and use of second-generation mediator-based sensors were among the improvements that were made to glucose biosensors in the 1980s. Manufactured printed test strips for SMBG were also made available [50,51,59-62]. Modified electrodes and customised membranes were used to enhance sensor effectiveness. The very first pen-sized, electrochemical blood glucose analyzer for diabetic individuals, the ExacTech, was introduced by Medisense Inc. in 1987[60]. It made use of a ferrocene precursor and GDH-PQQ. The healthcare system for diabetic patients underwent a dramatic shift as a result of ExacTech's accomplishment. Currently,

the majority of commercial glucose biosensors function similarly to the ExacTech metre. For self-monitoring glucose, they use ferrocyanide or ferrocene mediators.

Enhancing electron transport between the electrode surface and the redox centre of glucose oxidase (GOx) has been done in a number of ways. These include chemically altering GOx with electron-relay groups, utilising nanomaterials as electrical connections, and enzyme networking of GOx using redox hydrogels that conduct electrons [48, 63–65].

THIRD-GENERATION OF GLUCOSE BIOSENSORS

Because they allow for direct electron transfer among the enzyme and the electrode, third-generation glucose biosensors eliminate with the necessity for harmful mediators. The application of organic conductive materials that consist of charge-transfer complexes rather than mediators facilitates this [66, 67]. Tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) is one such substance. The use of these biosensors have made it possible to create implanted, needle-style devices which can track blood sugar levels in vivo constantly. They may effectively regulate the electrical behaviour of pyrrole-quinolinequinone enzymes (GDH-PQQ) and flavoproteins (GOx). Increased selectivity with no mediators is advantageous for biosensors. On typical electrodes, only a small subset of enzymes, including peroxidases, have shown direct electron transport [62, 68]. 3rd generation sugar biosensors have also been tested using other direct electron transfer techniques, including oxidised boron-doped diamond electrodes [71], the GOx/polypyrrole system [66, 69, 70], and TTF-TCNQ with a tree-like crystal structure [66, 67].

CONTINUOUS GLUCOSE MONITORING SYSTEMS (CGMS)

The idea of continuous tracking of blood sugar concentration was initially put out in 1975 [72], and in vivo glucose measurement was first illustrated in 1982 [52]. For improved diabetes management, constant glucose monitoring systems (CGMS) offer real-time data. Regular subcutaneous glucose monitoring and constant blood glucose metres are the two forms of CGMS presently in use. Nevertheless, direct determination of blood glucose is constrained in most CGMS due to electrode contaminant and the possibility of thrombosis. To combat this, needle-type electrodes that gauge interstitial fluid level of glucose and provide an estimation of blood glucose levels have been created [73–77].

The first under the skin implantable needle-type enzymatic electrode was presented in 1982 by Shichiri et al. [52]. Minimed (Sylmar, California, USA) created the first glucose biosensor with a needle for commercial use. The findings of the 72-hour analysis had to be retrieved at a medical facility, and it failed to deliver real-time data [78]. Nowadays, the Minimed Guardian REAL-Time system by Medtronic and Freestyle Navigator by Abbott are the highly used FDA-approved continuous glucose monitoring systems (CGMS) in needle-type design. These devices use temporary sensors that may be used for a period of 3 to 7 days and offer real-time glucose measurements that are updated every 1 to 5 minutes [79].

Utilising the microdialysis approach, which eliminates the need for direct contact among the transducer and the fluid in the interstitial space, continuous subcutaneous glucose monitoring may be accomplished [80, 81]. Devices using this methodology include GlucoDay and SCGM. In comparison to needle-type sensors, they offer greater precision, efficiency, and less signal drift [82, 83].

To be implemented successfully, in vivo CGMS must, however, adhere to a number of criteria, including biocompatibility, calibration, durability, accuracy, linearity, and miniaturisation. Although CGM has been suggested to help people with type 1 diabetes improve their blood sugar control [84–86], the therapeutic utility of CGMS has not yet been shown [87].

NON-INVASIVE GLUCOSE MONITORING SYSTEM

A significant amount of research has been put into creating less disruptive blood sugar analysis, which is a primary objective of sugar sensor technology. Laser modalities are the frequently used non-invasive blood sugar concentration detection techniques [88,89]. Light's characteristics in the fluid that's surrounding the interstitial space or anterior portion of the retina are used by laser sugar sensors. optical coherence tomography [94], Polarimetry [90], Raman spectroscopy [91], infrared absorption spectroscopy [92] and photoacoustics [93], and are a few examples of these techniques.

The GlucoWatch Biographer developed the very first sugar sensor authorised by the United States FDA department that used transdermal removal of interstitial fluid by reverse iontophoresis. It was developed by Cygnus, Inc. in Redwood City, California, in the United States. However, due to problems such a protracted warm-up period, false alarms, inaccuracy, skin irritation, and vulnerability to perspiration, this watch-like gadget only received a limited amount of commercial acceptability. As a result, it was discontinued in 2008. It has taken a lot of work, but there is still no reliable non-invasive way to measure glucose levels.

GLUCOSE BIOSENSORS FOR PONT-OF-CARE TESTING (POCT)

Because POCT (Point-of-Care Testing) is more affordable and produces findings more quickly than tests performed in laboratories, it is frequently used to assess blood

glucose levels in inpatient as well as outpatient environments. The majority of disposable enzyme electrode test strips used by POCT glucose biosensors [28] are constructed of either plastic or paper and include GOx, GDH-PQQ, GDH-NAD, or GDH-FAD enzymes with a redox mediator [33]. The procedure is placing an examination strip into the device, utilising a lancing tool to extract a little droplet of blood from the finger, and putting it to the testing strip. The IFCC (International Federation of Clinical Chemistry)-recommended conversion coefficient is then used to show the data as plasma glucose equivalents [95].

With its lightweight glucose biosensors, ExacTech has seen tremendous profitability since its establishment in 1987. Numerous electronic devices have since been released all around the world. According to the 2010 Diabetes Forecast Resource Guide, there are 56 distinct point-of-care (POC) glucose sensors offered in the US market by 18 different businesses. The market, however, is dominated by four large businesses: Abbott, Bayer, LifeScan, and Roche. Most devices take a little blood sample in the range of 0.3 to 1.5 microliters and may produce results in less than 10 seconds. They are calibrated according to plasma-blood levels.

ANALYTICAL PERFORMANCE VALIDATION OF GLUCOSE BIOSENSORS

Sugar biosensors are simple to use, only need a tiny amount of blood, and deliver findings quickly. Inaccurate measures, however, can have negative effects on patients, increasing morbidity and death. A few recommendations for quantitative accuracy requirements have been made to guarantee dependable performance. For glucose readings ranging from 1.6 to 25 mmol/L, the American Diabetes Association (ADA) originally proposed guidelines in 1994, which suggested a maximum allowed bias of under ten percent relative to reference techniques [97]. This cutoff point was further

lowered to less than 5% in 1996 [98]. For sugar values between 1.70 and 22.9 mmol/L, the FDA advises that blood sugar monitors ought to exhibit an error rate of below twenty percent when compared with standard laboratory results. The analytical objective was further lowered in 1996 to less below 5% [98]. For glucose values within 1.65 and 22 mmol/L, the U.S. FDA suggests that sugar sensors be flawed of no more than twenty percent when compared with standard laboratory results. Blood glucose guidelines are adviced by the International Organisation for Standardisation (ISO) 15197:2003, with varying specifications for values below and over 75 mg/dL. 95 percent of the person's glucose findings for blood sugar levels below 75 mg/dL should be within range of 0.88 mmol/L (16 mg/dL) of the device manufacturing company measuring techniques. The need is within 21% for sugar levels of 76 mg/dL or above.

To verify the analytical capability of the majority of glucose sensors, healthcare providers adhere to the CLSI recommendations. To certify the reliability and precision of glucose monitors over a range of glucose levels, the ISO Technical Committee ISO/TC 212 has developed the ISO 15197 guideline [99]. These guidelines stress the value of testing glucose biosensors in actual applications and provide the criteria and steps for the intended consumers to confirm and validate the operation of in vitro glucose monitoring systems.

For POC sugar biosensors employing capillary whole blood, the FDA guidelines include suggestions for research plans, statistical analyses, and presentations. These recommendations are consistent with ISO 15197 for reliability, precision, and assessments of user satisfaction [99].The parts 7.1–7.5 [99–101] of the recommendations can be summed up as follows.

PRECISION

Repeatability

Measurements were made at 5 distinct sugar levels between 35 and 420 mg/dL in order to assess repeatability. The exact same user, monitor, and reagents lot should be used to complete this in just one working day. A minimum of 10 glucose monitors and 500 reagent system units were required. Blood from a vein is the recommended sample. The specimens were maintained within 3 °C of the baseline temperature throughout the trials after being equilibrated at a temperature of 22 °C. Ten measurements were made for each sample per device. Based on the 10 measurements, each device average value, SD, and CV are computed. The sum of the variance, the pooled SD with a 95% CI, the combined CV, and the overall mean was then computed.

Intermediate Precision

The phrase "intermediate precision" describes the accuracy of test results obtained when the same procedure is applied to similar test objects in the same place, but with differences in other elements such as administrators, apparatus, calibration, ambient conditions, as well as time spans. Control samples at three distinct concentrations—32–52 mg/dL, 98–146 mg/dL, and 282–422 mg/dL—are used to assess intermediate accuracy in glucose assays. The assessment spans a minimum of ten days and covers a variety of devices and customers. At least 10 devies and 300 reagent system units are needed for the evaluation. A sample from each level of glucose is examined once day for 10 days using one of the 10 devices. Based on 10 measurements, mean, SD, and CV are estimated for every monitor. These measurements reveal details on the consistency and variability of a single system over several days. In order to evaluate the system's intermediate accuracy, other metrics such as the overall average (grand mean),

combined variance (pooled variance), combined SD (with a 95% CI), and combined CV are also calculated.

Accuracy

A least of 100 distinct participants should be included in the assessment procedure in order to evaluate system accuracy. Utilising capillary blood samples, the examination should be performed over a period of at least 10 days. The distribution outlined in Table 3 should be followed by the samples' glucose values. Each sample is measured a minimum of twice utilising two different monitors during the measurements. To accurately represent the systematic and haphazard mistakes that users may experience, the assessment should be conducted under realistic settings. The findings from a glucose biosensor are contrasted with standard glucose concentration readings from an instrument that is commercially and legally accessible. The paired standard test results and biosensor findings are compared, and the correlation coefficient, regression equation, and difference in plot analysis are computed for each set of data. The evaluation's goal is to make sure the biosensor operates properly and consistently under scenarios that are reflective of the usage for which it is designed.

TABLE 3. GLUCOSE CONCENTRATIONS OF SAMPLES FOR THE EVALUATION OF SYSTEM ACCURACY [99].

Percentage of samples %	Glucose concentration (mg/dL)
5	<50
15	50-80
20	80-120
30	120-200
15	201-300

10	301-400
5	>400

Linearity

Data collection entails acquiring two to four repetitions from five to eleven samples with various concentrations in order to test linearity in glucose biosensors. The dilution proportions or compositions can be used to determine how these concentrations relate to one another. Following that, correlation coefficients and equations for linear regression are computed by comparing the acquired data to known concentrations of glucose.

Consumer Effectiveness

Everyday use of sugar biosensors by individuals may cause difficulties that are not detected by experienced healthcare experts when they evaluate the glucose monitoring instruments [102]. The purpose of user evaluation of performance is to show how consumers can make utilisation of the sugar biosensors effectively and acquire accurate glucose readings while following the recommended directions and supplies provided with the equipment for training. The results from non-expert users are contrasted with those from healthcare experts using the same tools and samples and those from verified glucose testing techniques.

A least of 50 volunteers from various demographic groups (age, gender, and educational attainment) should be included in each batch of the devices. At least 3 separate reagents lot are used in user tests that are carried out across many locations. After reviewing the offered training materials, individuals use the devices to complete finger sticks and self-tests. Another blood sample is taken at the investigation location by a qualified healthcare expert immediately following the self-test. Within 5 minutes,

the second sample must be taken. Regression equations with confidence intervals are used to analyse the gathered data, and all of the data points are shown for visualisation. A comparison of user, professional, and reference findings is included in the outcomes.

Interferences

The accuracy of tests can be impacted by many different factors, including blood pressure readings, hypoxemia, low blood pressure, height from sea level, body temperature, and moisture. Electrochemical interferences in the blood that supply electrons not obtained from sugar can lead to falsely high glucose levels. Considering the sensor's maximum operational potential, interference molecules are electroactive chemicals. Uric acid, salicylic acid, dopamine tetracycline, etc. are only a few of the common interferents that the FDA has discovered [33].

Strip-based glucose tests are significantly impacted by hematocrit levels [103, 104]. In these tests, oxygen from red blood cells may prevent the redox mediator from utilising the enzyme GOx to harvest glucose-derived electrons. Furthermore, greater hematocrit values result in thicker blood, which slows down all component diffusion and decreases current in amperometric sensors [105]. Low hematocrit readings, which frequently indicate anaemia, might cause findings to be overstated. In point-of-care glucose biosensors, hematocrit is a significant cause of inaccuracy, especially in critical care units.

The precision of glucose biosensors can be affected by ascorbic acid, a common chemical [106,107]. Ascorbic acid is oxidised at the electrode surface in electrochemically based glucose biosensors, increasing the number of electrons produced and the amount of current produced. Ascorbic acid levels that are higher than normal may cause erroneously inflated glucose measurements. Depending on the

enzymes utilised, the technical procedures, or the design of the test strips, ascorbic acid's influence might vary.

Glucose, maltose, maltriose, maltotetraose, and icodextrin are all oxidised by the enzyme GDH-PQQ [108–110]. Yet point-of-care (POC) devices based on GDH-PQQ frequently overstate the amount of glucose in patients receiving icodextrin-based peritoneal dialysis [110,111]. The GDH-PQQ technique is hampered by the metabolization of isocodextrin into glucose polymers, predominantly maltose [Janssen et al. 110]. Icodextrin metabolites have been shown to create false elevations in blood glucose levels, which might result in hypoglycemia being misdiagnosed. In this high-risk group, physicians should be informed of this disruption and refrain from utilising glucose biosensors based on GDH-PQQ. POC glucose values should be tested again using a different diagnostic technology if they disagree with clinical diagnosis of hypoglycemia coma.

The levels of glucose can be disturbed by a number of medications [112]. Electrochemical biosensors may be affected by paracetamol, a commonly used drug used in both unintentional and purposeful poisonings[113]. Acetaminophen can cause disturbance on a biosensor when a large dosage is present by directly oxidising on the electrode surface after it passes through a porous membrane. A current is created by this oxidation, which raises the glucose measurement.

CONCLUSIONS

Diabetic patients' blood sugar concentrations are measured by utilizing glucose biosensors for evaluation, identification and therapy over the long term. New technological advances, including POC devices, CGMS, and noninvasive sugar monitoring methods have been invented in response to the increase in diabetes

patients. These types of biosensors are now commonly used for patient self-monitoring and point-of-care testing by healthcare providers. These biosensors' daily glucose readings allow for rapid and efficient blood glucose level adjustments.

Glucose biosensors have significantly improved, becoming more dependable, quick, precise, portable, and user-friendly. Improvements to technology including electrodes, membranes, immobilisation techniques, and nanomaterials are the subject of ongoing study. Despite significant advancements, obtaining accurate glucose monitoring still presents difficulties. Many POC devices fall short of the American Diabetes Association's (ADA) recommendation that a blood glucose point-of-care test have an accuracy within 5% of the detected value. When compared to techniques employed in central laboratories, biosensor technology is often less precise and reliable [114].

To guarantee accurate and dependable testing, a comprehensive examination of glucose biosensors is advised. Important quantitative requirements for appropriate hospital or residential point-of-care instruments include strong linearity, accuracy, and association with clinical laboratory standard techniques, as well as resilience to typical interferences. Following the manufacturer's recommendations for periodic calibration and assurance of quality is vital. The accuracy of data and therapeutic outcomes may be impacted by user-dependent variables such as incorrect use of test strips, a lack of quality control methods, filthy equipment, and unclean fingers. Studies have shown that education and ongoing training may minimise mistakes brought on by these variables and enhance measurement quality [115]. Therefore to enhance the performance of biosensors, it is important to focus on technical advancements, standardize analytical objectives, and implement ongoing evaluation and training for non-expert users.

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