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Reviewing evolutionary frontiers: Pioneering hyperglycemia detection for disease management

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ABSTRACT

Detection and diagnosis are pivotal processes in identifying and confirming diseases, often initiated through preliminary tests or screenings. Hyperglycemia, detected through blood glucose tests and symptom observation, is critically important not only in diabetes but also in various diseased states, including oncotherapy, where elevated blood sugar levels can exacerbate outcomes. Effective monitoring and control of blood glucose levels significantly enhance quality of life and reduce health risks. Managing prolonged hyperglycemia is closely associated with Diabetes Mellitus (DM), a pressing global health challenge contributing to an estimated 4.2 million deaths annually. India shoulders a substantial burden, with over 77 million adults currently diagnosed with diabetes, affecting both genders and showing varying prevalence across regions. Given its severe implications, timely and accurate detection is imperative. This review explains the evolution of glucose estimation techniques, tracing their progression from traditional urine-based tests to modern blood glucose monitoring devices. These advancements play a pivotal role in early detection and proactive management of diabetes, aiming to improve patient outcomes and alleviate the disease burden. Innovations like glucometers and continuous glucose monitoring systems have significantly enhanced patient care, leading to improved precision and control in glucose management.

Keywords: detection, hyperglycemia, diabetes, monitoring, patient care

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INTRODUCTION

Blood glucose monitoring and symptom assessment are crucial for the detection of hyperglycemia in cases of diabetes and other disorders where elevated blood sugar levels may exacerbate symptoms, such as pancreatitis, Cushing's syndrome, and severe infections [1, 2]. Prompt identification and monitoring enable effective therapy adjustments and reduce issues associated with these disorders [2]. Finding hyperglycemia is essential for managing diabetes because it makes it easier to diagnose, treat, and avoid consequences including cardiovascular disease and diabetic ketoacidosis. Patient quality of life is greatly enhanced and health risks are decreased for diabetics with proper blood glucose monitoring and control [3].

In patients with severe illnesses such as cancer, hyperglycemia is detected at different points in time: at the time of initial diagnosis, before therapy, during treatment, and after treatment. This is done to manage any pre-existing hyperglycemia and determine any long-term repercussions. Because of treatment-induced fluctuations, glucose monitoring must be done continuously while receiving active cancer treatment, especially chemotherapy, targeted therapy, or steroid treatment [4].

Therefore, a number of illnesses, such as diabetes mellitus, pancreatitis, Cushing's syndrome, severe infections, endocrine disorders, liver disease, chronic renal disease, stress and trauma, and hereditary disorders, can result in hyperglycemia. Moreover, hyperglycemia may result from tumor effects or side effects of treatment in certain malignancies, such as pancreatic, liver, colorectal, ovarian, breast, lung, and head and neck cancers [5-15]. All things considered, hyperglycemia can arise from a number of medical disorders, requiring careful assessment and specialized management techniques to maximize patient care and therapeutic results.

A major global health hazard, hyperglycemia linked to diabetes mellitus causes around 4.2 million fatalities per year [16]. This long-term illness impacts millions of people globally, and its occurrence is increasing at a concerning pace. With approximately 77 million adults in India already diagnosed with diabetes and that figure expected to rise to 134 million by 2045, the situation is especially dire [17]. This surge is in line with wider worldwide patterns that show a considerable increase in diabetes cases brought on by ageing populations, urbanization, and altered lifestyles [18].

Effective management and early detection of diabetes are crucial, given its severe complications, including cardiovascular diseases, neuropathy, retinopathy, and nephropathy [19]. Gender-specific prevalence data indicate that diabetes affects both males and females, with some regions reporting higher incidences among men and others among women [20]. This variation underscores the necessity of personalized diagnostic and management approaches to tackle this pervasive disease.

The evolution of glucose estimation techniques has been pivotal in improving diabetes diagnosis and management. Historically, glucose detection methods have transitioned from rudimentary urine-based tests to sophisticated blood glucose monitoring devices. Traditional urine tests, although widely used initially, were limited by their lack of accuracy and inability to provide real-time glucose levels [21].

The ability to precisely monitor and control blood sugar levels has been made possible by advances in technology, which have transformed the field of glucose estimation for both patients and healthcare professionals. The capacity to identify variations in blood glucose levels has been improved by innovations such CGM devices and glucometers, which allow for prompt interventions [22, 23]. In addition to helping patients achieve better results, these technological developments also lessen the overall toll that diabetes has on the world's healthcare systems [24]. In this review, we will examine the development of glucose estimate techniques over time, both technologically and historically. Through an analysis of these methods' development, this study underscores their pivotal function in the prompt identification and handling of diabetes, stressing the significance of ongoing innovation in this domain [25].

In the preliminary part of this review, we discuss the types of samples used for glucose quantification and the methods of their collection. The accuracy and reliability of these samples are crucial for effective diabetes management. The first section focuses on the historical perspectives of diabetes, tracing its recognition from ancient times to the modern era. The middle section explores the advancement of chemical methods for glucose detection, which laid the foundation for more sophisticated technologies. Enzymatic assays became the gold standard for laboratory glucose measurement due to their high specificity and sensitivity. The final section examines error control and time conservation through advanced glucose estimation methods using sensor technology. Glucometers revolutionized point-of-care testing by providing quick and accurate blood glucose readings. These sensor-based methods have minimized errors and reduced the time required for glucose estimation, significantly improving patient outcomes.

LITERATURE REVIEW

Historical overview of glucose estimation (BC to AD)

Before the modern era of scientific inquiry and laboratory techniques, glucose estimation relied on crude observational methods. Ancient civilizations recognized the sweet taste of urine as a symptom of certain diseases, including diabetes. Physicians in antiquity utilized taste tests and observations of urine characteristics for diagnostic purposes, laying the foundation for later developments in medical science (Table 1).

Tab. 1. Glucose detection methods during ancient civilizations

Era	Year	Methodologies & Developments	Description	Reference
BC	~1500 BC	Observation	Urine's sweet taste was noticed by ancient societies including the Greeks and Egyptians, who also connected it to specific illnesses	[26]
AD	1st century	Taste test	In the Roman era, doctors used the sweetness of urine to identify conditions like diabetes	[27]
AD	2nd century	Observation & smell	Prominent Roman physician Galen wrote about how diabetic patients' urine changed in taste and odor	[28]
BC/ AD	Various	Historical texts	Sweet urine has been observed as a symptom of sickness in numerous ancient medical writings and historical chronicles from different cultures	[29]

Historical review of glucose detection (Medical practices in varied cultures)

Ancestral civilizations recognized the sweet taste of urine as a possible sign of a number of disorders, including diabetes, and employed observational and sensory approaches as early means of glucose detection. In ancient times, medical techniques were not culturally universal, but a typical diagnostic technique was the observation of sweet urine (Table 2).

Methods of detecting glucose before 1840: Their evolution

Glucose detection methods before 1840 were rudimentary compared to modern techniques, but they laid the groundwork for future advancements. Table 3 summarizes some of the key developments in glucose detection before 1840: Optical characteristics and chemical reactions were the main focus of glucose detection techniques prior to 1840. Sugar concentrations were measured and their optical activity was understood with the help of the polarimeter and saccharimeter. These early innovations cleared the path for later, more advanced methods.

Samples used to detect glucose estimation

The glucose detection is essential for the diagnosis and treatment of several diseases, most notably diabetes mellitus. For the purpose of detecting glucose, a variety of sample types are available, each with specific benefits and uses. The following table 4 lists the several sample kinds that are frequently used to measure glucose, emphasizing their traits and uses in both clinical and scientific settings.

Tab. 2. Medical practices in varied cultures

Era	Year	Method/Discovery	Discovery	Reference
Ancient	~1500 BC	Observation	Ancient civilizations noted the sweet taste of urine as a symptom of certain diseases, possibly including diabetes	[26]
Ancient	1st Century	Taste test	Physicians in ancient Rome used taste tests of urine to diagnose diseases, including diabetes	[27]
Ancient	2nd Century	Observation & smell	Galen, a prominent physician in ancient Rome, described changes in urine odor and taste in diabetic patients	[28]
Ancient	Various	Historical texts	Numerous ancient medical texts mention the observation of sweet urine as a symptom of disease	[29]
Ancient	Various	Ayurvedic texts	Ancient Indian medical texts such as the Charaka Samhita mention the sweet taste of urine as a symptom of diabetes	[30]
Ancient	Various	Chinese medicine	Traditional Chinese medical texts describe the sweet taste of urine as a diagnostic indicator of disease	[31]
Ancient	Various	Islamic medicine	Medieval Islamic medical texts discuss the observation of sweet urine in the diagnosis of diabetes	[32]
Ancient	Various	Egyptian medicine	Ancient Egyptian medical papyri mention the sweet taste of urine and its association with illness	[33]
Ancient	Various	Greek medicine	Greek medical texts by Hippocrates and others discuss the significance of sweet urine in disease diagnosis	[34]
Ancient	Various	Roman medical practices	Various Roman medical texts and inscriptions provide insights into diagnostic practices involving urine	[35]

Tab. 3. Glucose detection methods before 1840

Year	Invention/Development	Description	Reference
1815	Polarimeter	Biot and Henry developed the polarimeter, allowing measurement of optical rotation caused by glucose	[36]
1816	Saccharimeter	Soleil and Mauméjean introduced the saccharimeter, a device for quantifying sugar concentrations	[37]

Tab. 4. An overview of the different samples used for glucose detection, along with their characteristics and applications

Sample Type	Description	Applications
Blood	Blood samples, obtained through venipuncture or fingerstick, are commonly used for glucose detection in clinical settings	- Diagnosis and management of diabetes
		- Monitoring glucose levels in hospitalized patients
		- Research studies requiring accurate glucose measurements
Urine	Urine samples, collected through voiding or catheterization, can provide valuable information about glucose excretion	- Screening for diabetes
		- Monitoring glucose levels in individuals with diabetes
		- Research studies investigating renal glucose handling
Saliva	Saliva samples, collected non-invasively through passive drooling or specialized collection devices, offer a convenient alternative for glucose monitoring	- Non-invasive glucose monitoring
		- Continuous glucose monitoring in home settings
		- Research studies on saliva-based diagnostics
Interstitial Fluid	Interstitial fluid samples, obtained through minimally invasive methods such as skin puncture, provide real-time glucose measurements using Continuous Glucose Monitoring (CGM) systems	- Continuous glucose monitoring in individuals with diabetes
		- Research studies on glucose dynamics and variability
		- Sports and exercise monitoring for athletes

Tears	Tear fluid samples, collected non-invasively using tear collection devices, are being explored for glucose monitoring due to their potential correlation with blood glucose levels	- Non-invasive glucose monitoring
		- Continuous glucose monitoring in individuals with diabetes
		- Research studies on tear glucose dynamics and tear film composition

Different sample types offer distinct advantages and applications for glucose detection, catering to the diverse needs of clinical practice and research. Blood samples remain the gold standard for accurate glucose measurement, particularly in clinical settings. However, non-invasive and minimally invasive sample types, such as urine, saliva, interstitial fluid, and tears, hold promise for convenient and continuous glucose monitoring, offering opportunities for improved patient comfort and accessibility. Continued research and technological innovation in sample collection and analysis methods will further enhance the utility and reliability of these sample types for glucose detection.

Chronological evolutionary detection methods of urinary glucose

The diagnosis and treatment of hyperglycemia, especially in diabetes mellitus, have greatly benefited by the use of urine glucose detection techniques. Glucosuria, or the detection of glucose in the urine, has proven a vital indicator of diabetes and other metabolic diseases. Urine glucose detection methods have substantially improved over time, moving from straightforward chemical assays to complex digital and wearable technology. The goal of developing these techniques was to improve accessibility, ease of use, and accuracy so that patients and healthcare providers could monitor and manage blood glucose levels more successfully. This progression highlights more general advances in science and technology that are meant to improve the identification, tracking, and treatment of diseases.

An outline of notable innovations and advancements in urine glucose detection techniques from the middle of the 1800s to the present is given in the following table 5. Every item provides a succinct explanation of the technique and its significance, highlighting the developments and advances that have influenced modern glucose monitoring procedures.

Tab. 5. Key Initial discoveries to modern technological advancements in the field of urine-based glucose detection

Year	Invention/Development	Description	Reference
1850s	First observations of glucosuria	Early studies identified the presence of glucose in urine as a sign of diabetes	[38]
1908	Benedict's test	A chemical test using Benedict's reagent to detect reducing sugars, including glucose, in urine	[39]
1941	Clinitest tablets	Tablets containing copper sulfate and other chemicals used to perform a simpler version of Benedict's test	[40]
1964	Glucose oxidase test strips	Development of enzyme-based test strips for glucose detection, using glucose oxidase	[41]
1970s	Multistix reagent strips	Introduction of multi-parameter test strips capable of testing for glucose and other analytes in urine	[42]
1990s	Automated urine analyzers	Machines capable of reading urine test strips and providing digital results	[43]
2010s	Smartphone integration	Test strips that can be read and analyzed using smartphone apps for improved accuracy and tracking	[44]
2020s	Wearable sensors	Development of wearable devices that continuously monitor urine composition for glucose and other biomarkers	[45]

The evolution of chemical approaches for detecting blood glucose

From straightforward chemical assays to complex enzymatic and electronic techniques, the glucose detection in blood and urine has undergone substantial change over time. The progress of chemical approaches for glucose detection from the middle of the 19th century to the present has shown in the table 6 with significant turning points.

Over the past two centuries, the field of glucose detection has seen remarkable advancements, from basic chemical reactions to sophisticated electronic sensors. These developments have revolutionized the management of diabetes, enabling individuals to monitor their blood glucose levels with greater accuracy, convenience, and efficiency. As technology continues to evolve, the future of glucose monitoring holds promises for further improvements in accuracy, accessibility, and patient care.

Evolution of enzymatic methods to detect blood glucose

The development of enzymatic glucose testing techniques has revolutionized hyperglycemia monitoring. Modern biosensors, which provide higher accuracy, sensitivity, and ease, have replaced outdated colorimetric assays. Detlev Müller's enzyme, glucose oxidase, is used in these contemporary methods to provide quick and accurate glucose measurements, which are critical for managing hyperglycemia. This development emphasizes how crucial enzymatic technology is to enhancing health outcomes and monitoring

The history of enzymatic glucose detection dates back to 1962, when the first enzyme electrodes were developed. More recently, wearable and continuous monitoring technologies have advanced, transforming glucose management without the need for glucose oxidase as shown in the table 7 in chronological order.

Tab. 6. Evolution of chemical methods to detect glucose

Year	Invention/Development	Description	Reference
1841	Fehling's solution	Fehling developed a copper sulfate-based solution to detect reducing sugars, including glucose, in liquids	[46]
1850s	Trommer's test	Trommer improved upon earlier tests using copper sulfate to detect glucose, forming a red precipitate	[47]
1883	Nylander's test	Nylander developed a bismuth-based reagent to detect glucose, producing a black precipitate	[48]
1885	Johnson's test	Johnson introduced a modification of Fehling's test using ammonium molybdate, improving sensitivity	[49]
1897	Haines' test	Haines modified Fehling's solution to improve stability and ease of use for glucose detection in urine	[42]
1908	Benedict's reagent	Benedict's test improved Fehling's solution for better accuracy in detecting glucose in urine	[43]
1923	Somogyi method	Somogyi developed a reagent that could detect and measure glucose in blood using an alkaline copper solution	[50]
1941	Clinitest tablets	Ames Company introduced Clinitest tablets for a simpler version of Benedict's test for urine glucose testing	[51]
1943	Folin-Wu method	This method used phosphomolybdic acid to measure blood glucose levels, providing more accurate results	[52]
1950s	Orthotoluidine method	Introduced a method using orthotoluidine for colorimetric glucose measurement in blood	[53]
1960s	Enzyme-based test strips	Introduction of glucose oxidase enzyme test strips for urine glucose detection, leading to Clinistix	[54]
1970s	Blood glucose test strips	Development of enzyme-based test strips for blood glucose testing at home, using glucose oxidase	[55]
1980s	Dextrostix and Ames reflectance meter	Introduction of blood glucose test strips (Dextrostix) and portable glucometers (Ames Reflectance Meter)	[56]
1990s	Amperometric glucose sensors	Use of electrochemical sensors with glucose oxidase for more accurate blood glucose readings	[57]
2000s	Continuous Glucose Monitoring (CGM)	Development of continuous glucose monitors using glucose oxidase-based sensors for real-time monitoring	[58]
2010s	Non-Invasive Glucose Monitoring	Research into non-invasive glucose monitoring methods, including optical and transdermal techniques	[57]
2020s	Advanced CGM and wearable sensors	Advances in CGM technology, including implantable sensors and integration with smartphone apps	[58]

Tab. 7. Evolution of historical enzymatic methods for the detection of glucose

Year	Invention/Development	Description	Reference
1920s	Discovery of glucose oxidase	The enzyme glucose oxidase was identified; it oxidises glucose specifically to produce hydrogen peroxide and gluconic acid	[61]
1962	First enzyme-based Test strip	Clinistix, the first glucose test strip with glucose oxidase and peroxidase, was released by Ames Company	[59]
1970s	Blood glucose test strips	Creation of blood glucose test strips with an enzyme base that include glucose oxidase for individual use	[65]
1980s	Glucometers with test strips	Enzyme-based test strips were utilized by portable glucometers to measure blood glucose levels at home	[60]
1990s	Amperometry sensors	Enhanced accuracy and usability with the development of electrochemical sensors utilizing glucose oxidase	[61]
2000s	Continuous glucose monitors	Implementation of real-time continuous glucose monitoring systems with glucose oxidase-based sensors	[62]
2010s	Smartphone integration	For improved management, enzyme-based glucose test strips that may be read and analyzed via smartphone apps	[63]
2020s	Wearable and implantable sensors	Implantable glucose oxidase sensors and sophisticated continuous glucose monitors are available for continuous monitoring	[64]

Sensor based technologies

Sensor-based technologies have played a pivotal role in the evolution of medical diagnostics, particularly in glucose monitoring for diabetes management. From the pioneering work of L. Umezawa et al. in the 1950s to the development of advanced Continuous Glucose Monitoring (CGM) systems in the present day, sensor technologies have continuously advanced, providing innovative solutions for real-time, continuous monitoring of glucose levels. The table 8 below outlines the chronological evolution of sen-

sor-based technologies for glucose monitoring, highlighting key milestones and developments. Each entry includes the year of the development, a brief description of the technology or discovery.

Tab. 8. Evolution of sensor-based technologies for glucose estimation

Year	Technology	Description	Reference
1956	pH electrode	Development of the first pH electrode by L. Umezawa et al., laying the foundation for electrochemical sensors	[65]
1962	Electrochemical glucose sensors	Clark and Lyons developed the first enzyme-based glucose sensor using glucose oxidase and a Clark electrode	[66]
1975	Amperometry biosensors	Commercialization of amperometry biosensors, including glucose sensors, by Yellow Springs Instrument Company	[67]
1987	Continuous Glucose Monitoring (CGM)	Development of the first commercial CGM system by Mini Med Inc., enabling continuous monitoring of glucose levels	[68]
1990s	Nanotechnology-based sensors	Introduction of nanotechnology-based sensors, enhancing sensitivity and specificity in glucose monitoring	[69]
2000s	Smartphone-connected sensors	Integration of glucose sensors with smartphone apps for real-time data monitoring and analysis	[70]
2010s	Wearable and implantable sensors	Development of wearable and implantable sensors for continuous glucose monitoring, enhancing user convenience	[71]
2020s	Advanced CGM systems	Introduction of advanced CGM systems with improved accuracy, stability, and integration with insulin delivery systems	[72]

The creation of Continuous Glucose Monitoring (CGM) devices and the invention of pH electrodes are just two examples of the many ways that sensor-based technologies have advanced over the years. With the ability to provide patients with real-time glucose level data, these innovations have completely changed the way diabetes is managed and have improved outcomes and quality of life throughout treatment. Future developments in this sector are made possible by the amalgamation of nanotechnology, wearable sensors, and smartphone connectivity, which has improved glucose monitoring's efficacy and accessibility.

Future challenges

Biomedical research, clinical diagnostics, and glucose monitoring for the treatment of diabetes all depend on the ability to detect glucose in biological materials. New techniques and tools for detecting glucose with better sensitivity, specificity, and usability have been developed as a result of recent developments in sensor technology. With an emphasis on significant advancements and matching references, table 9 offers an overview of significant research on glucose detection in biological samples.

Tab. 9. Future challenges in the glucose estimation

Year	Research Work	Description	Reference
2018	"A highly sensitive electrochemical glucose sensor"	Creating a novel electrochemical sensor for ultrasensitive glucose detection using gold nanoparticles and graphene oxide	[73]
2019	"Fluorescent nanoparticles for non-invasive glucose monitoring"	Formulation of fluorescent nanoparticles for non-invasive near-infrared spectroscopy glucose monitoring in biological fluids	[74]
2020	"Implantable glucose biosensors for continuous monitoring"	Enhancing stability and biocompatibility of implantable glucose biosensors to enable continuous glucose monitoring	[75]
2021	"Paper-based microfluidic devices for point-of-care glucose testing"	Manufacturing of paper-based microfluidic devices for quick and affordable point-of-care glucose monitoring in medical environments	[76]
2022	"Nanowire-based sensors for real-time glucose monitoring"	Research on very sensitive nanowire-based sensors for monitoring glucose levels in biological samples in real time	[77]

Novel approaches and tools for glucose detection have been developed recently; these could find use in glucose monitoring, clinical diagnostics, and biological research. Novel electrochemical sensors, fluorescent nanoparticles, implantable biosensors, and paper-based microfluidic devices are a few of these developments that show promise for real-time glucose monitoring in a variety of biological samples. For glucose detection systems to become even more accurate, dependable, and accessible and eventually assist the biomedical research and healthcare communities' further study in this area is imperative.

New issues that need to be resolved in order to further enhance accessibility, sensitivity, and accuracy of glucose detecting technologies are emerging. Directions for future study and improvement in the field of glucose monitoring must be guided by an understanding of these obstacles (Table 10).

Tab. 10. The table below outlines key future challenges in the detection of glucose, along with corresponding references for further exploration

Challenge	Description	Reference
Enhanced sensitivity	Achieving higher sensitivity in glucose detection methods to accurately measure low concentrations of glucose, particularly in interstitial fluid	[78]
Selectivity and specificity	Improving selectivity and specificity to accurately differentiate glucose from other interfering substances present in biological samples	[79]
Continuous monitoring	Developing technologies for continuous glucose monitoring that provide real-time data without the need for frequent calibration and interventions	[80]
Biocompatibility and long-term stability	Ensuring the biocompatibility and long-term stability of implantable glucose sensors to minimize tissue reactions and maintain accuracy over time	[81]
Miniaturization and integration	Miniaturizing glucose sensing devices and integrating them into wearable and portable platforms for convenient and unobtrusive monitoring	[82]
Cost-effectiveness and accessibility	Enhancing the cost-effectiveness and accessibility of glucose monitoring technologies to ensure affordability and widespread adoption	[83]

The detection of glucose in the future will have to overcome a number of obstacles, such as the requirement for improved sensitivity, selectivity, and continuous monitoring capabilities in addition to maintaining biocompatibility, stability, and affordability. It will take interdisciplinary teamwork as well as creative solutions in sensor design, materials research, and data analytics to overcome these obstacles. The development of next-generation glucose monitoring devices that provide better accessibility, accuracy, and convenience for people with diabetes and other glucose-related illnesses will be made possible by overcoming these challenges.

CONCLUSION AND SUMMARY

The development of glucose detection is a reflection of the ongoing innovation and technology and scientific method adaption to satisfy the demands of biomedical research and healthcare. The development of glucose detection from simple techniques to complex sensor technologies highlights the value of interdisciplinary cooperation and technical innovation in enhancing medical results.

CONFLICTS OF INTEREST

Authors declared no conflicts of interest.

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