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Review Article

Salivary Glucose as a Potential Biomarker for Monitoring Blood Glucose Levels in Type 2 Diabetes Mellitus: Current Insights and Future Prospects

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ABSTRACT

Monitoring glucose levels is crucial for effectively managing diabetes mellitus, a prevalent and chronic metabolic disorder impacting millions worldwide. Traditionally, blood glucose level tests have been the gold standard for diagnosing and managing diabetes. However, alternative methods such as salivary glucose level tests have gained attention. One significant advantage of salivary glucose level tests is their non-invasive nature, which eliminates the need for finger pricking or venous blood collection which may increase patient compliance, Additionally, salivary glucose level tests offer the potential for real-time or continuous monitoring, enabling timely adjustments in diabetes management strategies. However, several challenges need to be addressed before salivary glucose level tests can be widely adopted. Saliva glucose levels are influenced by various factors, including oral health, diet, and saliva flow rate. Standardization of saliva collection methods and the development of reliable and accurate sensing technologies are crucial to overcome these limitations. Moreover, obtaining regulatory approval and conducting validation studies is imperative to affirm the clinical efficacy of tests measuring salivary glucose levels. In conclusion, tests measuring salivary glucose levels present a promising alternative to conventional blood glucose tests in the realm of diabetes management. While addressing technical and clinical challenges requires additional research, the appealing non-invasive nature and the potential for frequent monitoring make salivary glucose level tests an attractive option for enhancing diabetes care. Future advancements in salivary glucose sensing technologies may revolutionize glucose monitoring, improving the quality of life for individuals with diabetes.

Keywords: Hyperglycemia, Salivary Glucose Level, Non-invasive.

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INTRODUCTION

Diabetes, a chronic metabolic disorder marked by hyperglycemia resulting from deficiencies in insulin secretion, insulin action, or both, stands among the leading causes of global mortality.[1] Those afflicted with diabetes face increased susceptibility to infectious diseases, likely attributed to compromised immune systems.[2] Prolonged hyperglycemia in diabetes inflicts enduring harm and dysfunction on vital organs such as the eyes, kidneys, nerves, heart, and blood vessels. Manifestations of chronic hyperglycemia encompass polyuria, weight loss, polydipsia, occasional polyphagia, blurred vision, and impaired growth.[1]

Diabetes is classified into three primary types: type 1 diabetes, type 2 diabetes, and Gestational Diabetes Mellitus (GDM). Type 1 diabetes is a cellular-mediated autoimmune β-cells destruction of the pancreas usually results in absolute insulin deficiency.[3] Type 1 diabetes, often referred to as juvenile diabetes, typically manifests during childhood or adolescence, necessitating insulin injections for managing blood sugar levels in affected individuals.[4] Approximately 85-90% of patients have type 2 diabetes, which can manifest as predominant insulin resistance with relative insulin deficiency or predominant insulin resistance alongside defective secretion.[3,5] GDM is identified as a condition involving varying degrees of glucose intolerance, with its onset or initial recognition occurring during pregnancy.[6] It can be diagnosed during the second or third trimester of pregnancy and typically resolves post-childbirth. Nevertheless, women with a gestational diabetes history are at an elevated risk of developing type 2 diabetes later in life.[1,4] There are various specific types of diabetes, including monogenic diabetes syndromes (such as neonatal diabetes and Maturity-Onset Diabetes of the Young [MODY]), endocrinopathies (e.g., Cushing syndrome, pheochromocytoma), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), diabetes induced by drugs or chemicals (such as glucocorticoids used in the HIV/AIDS treatment or post-organ

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transplantation), and rare forms of autoimmune-mediated diabetes.[3]

Effective healthcare management relies on accurate diagnosis and continuous monitoring, shaping treatment decisions and enabling healthcare providers to track patient progress with precision.[7] Timely identification and intervention are vital in preventing complications such as retinopathy (leading to blindness) and peripheral neuropathy (raising the risk of foot ulcers, Charcot arthropathy, and amputation). Autonomic neuropathy may result in gastrointestinal, cardiovascular, genitourinary issues, and sexual dysfunction.[3] Currently, diabetes diagnosis and monitoring involve a blend of laboratory analyses, clinical examinations, and medical history assessments, focusing on identifying elevated blood glucose levels through various methods. Standard blood glucose tests comprise i) the fasting blood glucose test, which analyzes glucose levels after an 8 hr fasting period to assess baseline glucose levels; ii) the random blood glucose test, providing immediate insights into blood glucose levels at any point during the day, irrespective of the patient's last meal; and iii) the oral glucose tolerance test, a comprehensive examination that assesses glucose levels before and 2 hr after the consumption of a sugary beverage, helping healthcare providers evaluate the body's ability to regulate glucose over time and identify potential glucose tolerance issues.[4]

Diabetes Mellitus can be diagnosed based on specific criteria: an HbA_{1c} level of ≥6.5%, random plasma glucose level ≥200mg/dL, fasting plasma glucose level ≥126mg/dL, or OGTT 2 hr glucose in venous plasma ≥200mg/dL. Impaired Fasting Glucose is indicated by fasting glucose levels ranging from 100-125mg/dL in venous plasma. Impaired Glucose Tolerance is identified when 2 hr plasma glucose during OGTT falls between 140-199mg/dL with fasting glucose <126mg/dL. For Gestational Diabetes, the diagnostic criteria according to the HAPO study specify that gestational diabetes is indicated if any one of these values is exceeded, in contrast to the previous guidelines that required exceeding at least two values.[5]

Recent epidemiological surveys have revealed that an HbA_{1c} level ≥6.5% demonstrates a specificity significant enough to justify diagnosing diabetes, while an HbA_{1c} level <5.7% is adequate to exclude a diagnosis of diabetes.[3] Compared to Fasting Plasma Glucose (FPG) and Oral Glucose Tolerance Test (OGTT), A1C offers various advantages, such as increased convenience (eliminating the need for fasting), enhanced preanalytical stability, and reduced susceptibility to daily fluctuations caused by stress and illness. These benefits must be weighed against higher costs, the inaccessibility of A1C testing in impoverished regions, and the skewed connection between A1C and average glucose in specific individuals. Therefore, when utilizing A1C for diabetes diagnosis, it is crucial to take into account factors such as age, race, and the presence of anemia/hemoglobinopathies.

It is recommended to promptly repeat the same test with a new blood sample for confirmation. This is particularly important unless there is a definitive clinical diagnosis, such as a patient experiencing a hyperglycemic crisis or exhibiting classic symptoms of hyperglycemia, along with a random plasma glucose level of 200 mg/dL. For instance, if the A1C is 7.0% and a follow-up result is 6.7%, diabetes is officially diagnosed. This further supports the diagnosis if the results of two distinct tests, such as A1C and FPG, are both above the diagnostic cutoff. On the other hand, if a patient's results from two separate tests are inconsistent and exceed the diagnostic cutoff point, it is avisable to repeat the test.

The term "prediabetes" is used to describe people with Impaired Glucose Tolerance (IGT) and/or Impaired Fasting Glucose (IFG), which suggests an elevated risk for the development of diabetes in the future. IFG and IGT should be considered risk factors for CVD and diabetes rather than as distinct clinical entities. Obesity (particularly visceral or abdominal obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension are all linked to IFG and IGT.[1]

Diabetes Mellitus is a silent epidemic, where the number of cases grows steadily, and early detection is crucial to ensure a better prognosis and prevent clinical complications.[8,9] Globally, there is widespread accessibility to urine and blood tests for the screening, prognosis, diagnosis, and monitoring of DM. Although urine and blood samples can be used to estimate glucose levels, there are several challenges associated with the process. For example, the presence of glucose in urine may not be detectable in the early stages of diabetes; it becomes evident only at advanced stages. In contrast, venous blood sampling can be more invasive than capillary blood sampling, so patients might feel uncomfortable and inconvenienced. Furthermore, long-term diabetics who suffer from diabetes experience difficulty in collecting blood with needles or lancets due to finger lumps, infection risk, and poor peripheral circulation, which disrupt daily life, induce nervousness, and make the process difficult to accomplish.[10] A far more straightforward, noninvasive, reliable, and less expertise-requiring method for the diagnosis and monitoring of diabetes is highly desirable because regular blood glucose testing creates unnecessary discomfort and mental distress for patients.[11]

Saliva and its Glucose Monitoring Techniques

Saliva

Saliva is an exocrine fluid secretion that reflects both local and systemic changes. It acts as the mouth's primary defense mechanism and contains a variety of proteins, including enzymes, immunoglobulins, albumin, some polypeptides, and biomarkers that can be useful for diagnostic procedures.[12] Because the composition of saliva is influenced by a person's hormonal, neurologic, metabolic, and nutritional state, it has the potential to diagnose a variety of diseases and physiological conditions.[13,14]

Salivary analysis is a modern diagnostic technique that involves examining saliva to gain significant insights into an individual's state of health. This innovative diagnostic tool employs saliva samples to evaluate both oral and systemic health, enabling the detection of diseases, monitoring treatment effectiveness, and tailoring healthcare approaches.

In dentistry, saliva testing plays a crucial role in diagnosing and monitoring oral conditions like dental caries, periodontal disease, and oral infections. Going beyond oral health, the potential of salivary analysis extends to the identification of systemic diseases. Researchers have pinpointed salivary biomarkers linked to a range of conditions, including diabetes (such as glucose levels), cardiovascular diseases, infectious diseases (such as HIV and hepatitis), cancer, autoimmune disorders, and neurological disorders (such as Alzheimer's and Parkinson's disease). These biomarkers provide valuable insights into the progression of diseases, responses to treatment, and the overall health of patients.[4]

Salivary Glucose Measurement (SGM)

Saliva contains glucose derived from the blood through passive diffusion and active transport mechanisms. A salivary enzyme called alpha-amylase from the glycoside hydrolase family, created by salivary glands, primarily parotid has been shown to rise in diabetics compared to non-diabetics and can be used as a diagnostic indicator. Its purpose is to break down large molecules like starch and carbohydrates. It serves as a marker for the diagnosis of diabetes when it is found to be significantly higher in diabetics than in non-diabetics, leading to excessive glucose production. A few studies have also suggested that reducing the absorption of complex carbohydrates may help to control blood sugar levels while using a salivary alpha-amylase inhibitor.[2] Studies have demonstrated elevated salivary MDA levels and decreased salivary TAC and GPx levels in patients with diabetes. Salivary fructosamine levels have proven to be closely linked to blood fructosamine levels, making it a dependable biomarker for diagnosing and monitoring diabetes.[15] Recent research has identified salivary oxidative stress biomarkers, including Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), and Glutathione Peroxidase (GPx), as valuable indicators of an individual's oxidative stress status, which is relevant in diabetic conditions.[16] Hence, in reflecting the status of the individual physiologically and providing a diagnosis for diseases, saliva is therefore functionally comparable to blood.

Saliva biomarkers have long been recognized for their potential to provide valuable insights into a person's overall health. However, using salivary glucose as a diagnostic tool for Diabetes Mellitus (DM) has been met with challenges, primarily due to the ongoing debate surrounding the relationship between salivary glucose levels and blood glucose levels.[17] While some studies suggest a positive connection between salivary glucose and blood glucose levels in individuals with DM, indicating the possibility of salivary glucose serving as a marker for DM detection conflicting findings have arisen.[18,19] Certain research studies have failed to establish a significant correlation between salivary glucose and blood glucose levels.[20,21] This divergence in research outcomes can be attributed to the diverse methods employed in saliva collection.

Saliva collection

Saliva is complex and diverse, originating from major glands like the parotid, submandibular, and sublingual glands, rather than being a uniform bodily fluid. Each of these glands produces distinct types of saliva. Additionally, minor salivary glands, gingival crevicular fluid, and debris contribute to this intricate composition.[22]

Saliva analysis employs two primary categories: whole saliva, which includes secretions from all salivary glands, and single-gland saliva. These samples can be obtained through either stimulated or unstimulated methods.[23] Unstimulated saliva collection, where individuals naturally accumulate saliva in their mouths without external intervention, is the preferred choice for most analyses due to its ease, non-invasiveness, and adaptability across various applications.

On the other hand, stimulated saliva collection is achieved by encouraging chewing or using taste stimulants like citric acid, enhancing salivary flow and thus providing increased saliva volume for analysis. This is valuable when studying specific elements in higher concentrations under stimulated conditions or requiring larger saliva amounts for in-depth research.[4]

Additionally, in certain specialized cases, it becomes crucial to obtain saliva from particular salivary glands. This targeted approach allows researchers to explore biomarkers unique to individual glands, providing valuable insights into gland-specific functions and conditions. Tailoring saliva collection methods to the specific research requirements ensures accurate and comprehensive analysis in various scientific investigations. These variations in saliva collection methods and the resulting composition underscore the critical influence of both the collection technique and the specific location of saliva sampling.[24,25]

Understanding the complexities of saliva composition and recognizing the significance of varied collection methods are crucial steps toward unraveling the potential of salivary glucose as a reliable diagnostic indicator for DM.

Advantages of SGM

Salivary Glucose Measurement (SGM) offers several notable advantages for individuals with diabetes. Firstly, it provides a non-invasive and painless method for measuring glucose levels in saliva, eliminating the discomfort associated with needles or finger pricks.[11] This makes the monitoring process more

comfortable and less intimidating, especially for individuals who are needle-phobic or children.

Additionally, SGM is highly convenient and user-friendly.[12] Individuals can easily collect saliva samples without the need for specialized equipment or assistance, enhancing the overall experience of regular glucose monitoring. Moreover, SGM reduces the risk of infections, as it does not involve any invasive procedures, making it a safer option, particularly for individuals with weakened immune systems.

One of the significant benefits of SGM is its potential for continuous monitoring. Evolving technologies enable real-time tracking of glucose levels without the need for frequent tests, providing continuous data for better diabetes management. Another advantage is that SGM does not require dietary restrictions during sample collection, allowing for a more natural representation of glucose levels, even after meals.

MATERIALS AND METHODS

The data were gathered from a comprehensive search of 17 research studies published within the past 5 years to ensure the most recent and relevant information. The search encompassed reputable databases such as PubMed, Science Direct, Cureus, and Google Scholar. The search terms utilized were "salivary glucose," "type 2 diabetes mellitus," "blood glucose," and "non-invasive methods in T2DM." The information retrieval process involved thorough examinations of text and tables within the selected studies. Data extraction focused on key elements, including the number of patients involved in each study, the correlation between salivary glucose and blood glucose levels, and the identification of salivary glucose as a potential biomarker. Rigorous review procedures were implemented to ensure the accuracy and reliability of the extracted information.

Each study's methodology was reviewed to understand the specific techniques used for salivary glucose estimation and to identify any variations in collection methods. The research encompassed various aspects, including the assessment of optimal saliva collection techniques, exploration of salivary markers beyond glucose, and the correlation of salivary parameters with blood glucose levels in different contexts.

Additionally, the studies were critically evaluated for limitations and potential biases. Factors such as oral conditions, medication influences, and variations in salivary composition were taken into account. The need for standardization in salivary glucose estimation techniques was emphasized, and the studies underscored the necessity for further research to validate and extend the reported findings. Overall, this comprehensive review provides a synthesized analysis of recent advancements in understanding the role of salivary glucose as a potential biomarker for monitoring blood glucose levels in Type 2 Diabetes Mellitus. The review not only highlights the current state of knowledge but also underscores the gaps and opportunities for future research in this evolving field.

Challenges and Prospects

Challenges

Salivary Glucose Measurement (SGM) offers a promising non-invasive method for monitoring glucose levels in individuals with DM. However, this novel approach confronts various challenges that require resolution to seamlessly integrate it into diabetes management practices.

Ensuring Accuracy and Consistency

Achieving accurate and consistent salivary glucose measurements poses a challenge. It is essential to standardize the techniques and devices used for SGM to obtain reliable results, which are crucial for effective diabetes management.[2]

Interference from External Factors

Various factors like diet, oral hygiene, and medications can influence saliva composition, affecting glucose measurements. These factors create difficulties in obtaining precise and uncontaminated results.[1]

Saliva Composition Variability

Saliva composition varies significantly among individuals and even within the same person at different times. This variability makes it challenging to establish universal reference ranges and reliable baseline values for salivary glucose levels.[7]

Limited Clinical Validation

Despite its potential, SGM requires extensive clinical validation to confirm its accuracy and reliability in different diabetes-related scenarios. Comprehensive clinical studies are necessary to gain acceptance from medical professionals and regulatory authorities.

Integration with Existing Monitoring Methods

Integrating SGM with current diabetes management protocols, alongside traditional blood glucose monitoring, presents a challenge. Coordinating and merging data from various monitoring techniques to provide comprehensive insights for healthcare providers is essential for effective patient care.

Affordability and Accessibility

The affordability and availability of SGM devices can be barriers, especially in resource-limited settings. Ensuring that these technologies are economically viable and accessible to a broader population is crucial for their widespread adoption and effective diabetes management.[4]

Author	Study	Results
Choudhry AA *et al.*[8] Sep 2022.	To assess salivary glucose levels and Fasting Plasma Glucose (FPG) in healthy and diabetic individuals and to determine the relationship between salivary glucose and glycated hemoglobin (HbA_{1c}).	The study involving 200 participants reveals a notable contrast in salivary glucose levels between control and diabetic groups, with a proportional increase with higher FPG and glycated Hemoglobin (HbA_{1c}). Strong positive correlations were found between salivary glucose, FPG, and HbA_{1c}. Regression equations were derived to predict FPG and HbA_{1c} from salivary glucose. The study suggests that saliva can serve as an initial screening tool for diabetes, potentially replacing some invasive blood glucose tests in regular monitoring. However, limitations such as oral factors and medication influence need consideration, emphasizing the need for further research and standardization of salivary glucose estimation techniques.
Xiao Z *et al.*[27] May 2022	To investigate the link between salivary levels of Human β Defensin-2 (HBD-2) and LL-37, blood sugar, and periodontal health among individuals with T2DM.	The study explored the correlation between the expression levels of Human β Defensin-2 (HBD-2) and LL-37 in saliva with blood glucose and periodontal status in Type 2 Diabetes Mellitus (T2DM) patients. The research included 89 T2DM patients with Chronic Periodontitis (CP) and found that those with poor glycemic control and moderate to severe CP exhibited elevated expression levels compared to those with good glycemic control and mild CP. The study revealed a significant interplay between blood glucose, periodontal status, and saliva HBD-2 and LL-37 levels. Additional analysis of individual effects highlighted a positive synergistic impact of both blood sugar and periodontal status on the levels of HBD-2 and LL-37 in saliva, underscoring the potential involvement of these salivary markers in advancing periodontal inflammation in patients with T2DM. These findings contribute valuable insights for preventing and treating CP in individuals with T2DM, highlighting the importance of glycemic control in managing periodontal health.
Cui Y *et al.*[28] Mar 2022	To determine an optimal saliva collection technique and then utilize it to analyze the general and specific relationships between salivary and blood glucose levels in people with diabetes and healthy controls.	The study involved the collection of saliva and blood samples from 80 participants, including 40 Diabetes Mellitus (DM) patients and 40 healthy controls. Various collection methods were employed, and the association between salivary glucose and blood glucose levels was investigated. Unstimulated Parotid Saliva (UPS) method showed the highest correlation with blood glucose and was identified as the most promising for DM diagnosis. Subsequent analyses involved individual correlation studies, distinguishing between pre- and post-meal salivary glucose levels, and assessing the stability of individual correlations over a month. The study concluded that UPS collected before breakfast demonstrated potential as a non-invasive method for monitoring blood glucose levels in DM patients.
Shah VS *et al.* [2] Jan 2022	To investigate the levels of salivary amylase in type II diabetic patients.	The study, involving 80 participants aged 30 to 60, divided into three groups: Uncontrolled diabetics, Controlled diabetics, and Healthy controls, aimed to analyze salivary amylase levels in relation to diabetes. Inclusion criteria encompassed age and diabetes status, while exclusion criteria excluded severe complications or other illnesses affecting salivary amylase. Analyses revealed a significant correlation between age and diabetic groups, with blood sugar levels and glycated HbA_{1c} levels increasing significantly from healthy to controlled and uncontrolled diabetics. Salivary amylase levels were significantly elevated in individuals with diabetics compared to those without the condition, suggesting its potential as a biomarker for diabetes diagnosis and monitoring. The study emphasized the need for larger-scale research to validate these findings and explore the role of salivary amylase in dental caries among diabetics.

Author	Study	Results
Ganesan A *et al.*[13] Sep 2021.	To investigate the accuracy of employing salivary glucose in the diagnosis and monitoring of blood glucose levels in individuals with gestational diabetes and to connect blood glucose levels with stimulated and unstimulated salivary samples.	The study aimed to evaluate the reliability of salivary glucose levels as a diagnostic tool for gestational diabetes (GDM) in comparison to blood glucose levels. The research involved 199 participants, including healthy individuals and those with GDM. Blood samples and saliva were collected, and diverse analyses were employed to measure salivary glucose levels. The findings revealed elevated salivary and blood glucose levels in GDM patients, with a positive but moderate correlation between the two. Receiver Operating Characteristic (ROC) curve analysis indicated significant diagnostic validity for salivary glucose in fasting and postprandial states. The study concluded that saliva sampling is a safe and noninvasive alternative for GDM screening, suggesting further research with larger populations to establish specific salivary glucose levels for diagnosis and monitoring.
Pérez-Ros P *et al.*[29] Mar 2021.	To provide a summary of the research on the association between variations in salivary amylase and glucose levels.	The scoping review investigated the connection between salivary amylase levels and diabetes, analyzing 32 relevant articles up to October 2020. Findings revealed varied salivary amylase levels in diabetic individuals across studies, with some reporting higher levels and others lower. Factors such as sample characteristics and measurement techniques contributed to this variability. The review emphasized the need for standardized methodologies and larger studies to better understand the relationship. Despite limitations in study designs and populations, the research provided valuable insights into the complex link between salivary amylase and diabetes, calling for more comprehensive investigations in the future.
Hegde SS *et al.*[9] Nov 2020	To assess and correlate salivary candidal carriage, IgA levels, serum, and salivary glucose levels in people with and without diabetes.	The study involved 88 participants categorized into controlled diabetics, uncontrolled diabetics, and non-diabetics. Various parameters, including serum and salivary glucose levels, IgA levels, and Candida Colony-Forming Units (CFU), were analyzed. Uncontrolled diabetics exhibited the highest serum glucose levels, salivary glucose levels, and Candida CFU, while controlled diabetics showed higher serum and salivary IgA levels. Salivary glucose levels were suggested as a potential non-invasive tool for monitoring glycemic status and assessing salivary constituents that may aid in the diagnosis and management of oral issues in diabetes, such as a predisposition to oral candidiasis.
Jian C *et al.*[30] Jun 2020.	To assess salivary 1,5-AG's efficacy in screening Chinese individuals for diabetes.	The study aimed to assess the potential of salivary 1,5-Anhydroglucitol (1,5-AG) as a marker for diabetes. They included 641 participants categorized into non-diabetes and newly diagnosed diabetes groups. Saliva and serum samples were collected, and the study identified a notable reduction in salivary 1,5-AG levels among individuals with diabetes. The levels correlated negatively with fasting plasma glucose, 2 hr plasma glucose, and glycated hemoglobin A1c, with stronger correlations in diabetes subjects. Salivary 1,5-AG, particularly when combined with other markers, showed promise for efficient diabetes screening, potentially reducing the need for the oral glucose tolerance test. The study suggests salivary 1,5-AG could be a valuable tool for diabetes detection in the Chinese population.
Kumar A *et al.*[3] Jun 2020.	A Randomised Control Trial assessing the differences in serum and salivary glucose levels between people with diabetes mellitus and healthy people.	The study aimed to explore the correlation between salivary and serum glucose levels in diabetes. The research involved 200 subjects divided into groups based on diabetes type and a control group. Blood and saliva samples were collected, and glucose levels were analyzed. Results indicated a significant association between serum and salivary glucose levels in diabetic patients and controls. Salivary glucose was found to be elevated in diabetes patients compared to the control group. The study suggests that salivary glucose could serve as a non-invasive biomarker for early diabetes detection and monitoring, particularly for vulnerable populations.

Author	Study	Results
Gupta V *et al.*[31] May 2020.	Case-control study correlating the blood and saliva glucose levels of diabetic and healthy non-diabetic people and evaluating the effectiveness of saliva as a diagnostic tool.	The study investigates the potential of saliva as a diagnostic fluid for monitoring diabetes. Diabetes mellitus, characterized by elevated blood glucose levels, affects a significant portion of the population. The research aims to compare fasting and postprandial serum glucose levels with salivary glucose levels, evaluating saliva's potential as a diagnostic tool for diabetes. The study includes 90 participants, consisting of 45 healthy individuals and 45 previously diagnosed diabetic patients. Blood and saliva samples are collected during fasting and after a meal, and glucose levels are determined using the oxidase-peroxidase method. The findings indicate a notable positive correlation between blood and salivary glucose levels in individuals with DM. Limitations include variations in salivary composition and inconsistent glucose levels in different conditions.
Tiongco REG *et al.*[32] July 2019.	To identify whether salivary glucose, amylase, calcium, and phosphorus may be used as non-invasive diagnostic indicators of DM.	The study conducted in Angeles City, Philippines, involved 80 participants, including non-diabetic and diabetic individuals, to assess the diagnostic potential of salivary biomarkers in diabetes. Utilizing the Mann-Whitney U test, the research revealed that diabetic participants exhibited significantly higher levels of salivary glucose and salivary amylase compared to non-diabetics. Notably, salivary glucose and amylase showed promise as indicators, demonstrating a positive association with FBG. This positive association suggests that salivary glucose could serve as a noninvasive tool for monitoring glycemic status in diabetic patients. However, the study emphasizes the necessity for further research to validate and extend these findings, underscoring the importance of additional studies to confirm the clinical relevance and reliability of salivary biomarkers.
Mishra N *et al.*[33] April 2019.	To determine whether glycemic status can be measured noninvasively using saliva rather than an intrusive procedure in T2DM patients.	The study involved 100 T2DM patients and 100 healthy individuals, with a focus on assessing the correlation between salivary glucose, blood glucose levels, and the presence of Candida albicans in the oral cavity. Salivary glucose levels were measured enzymatically, and blood glucose levels were obtained through venipuncture. The findings revealed a significant correlation between salivary and blood glucose levels, indicating a potential for using salivary glucose as a noninvasive method for tracking glycemic status in individuals with diabetes. Moreover, the study observed higher salivary candida carriage in individuals with uncontrolled diabetics compared to those with controlled diabetics and healthy individuals, suggesting a link between oral candidal colonization and blood glucose levels. This reinforces the clinical significance of salivary analysis in assessing the health status of diabetic patients.
Ragunathan H *et al.*[34] 2019.	To calculate salivary glucose levels and compare them to blood sugar.	The study aimed to investigate the correlation between serum and salivary glucose levels in patients with diabetes and those without diabetes. The inclusion criteria designated diabetic patients as cases and non-diabetic individuals as controls, with pregnant females, tobacco users, and those with systemic ailments being excluded. Serum and salivary glucose levels were measured using the Glucose Oxidase-Peroxidase (GOD-POD) method. The results indicated a statistically significant correlation between serum blood glucose and salivary glucose levels, with diabetic patients exhibiting higher salivary glucose concentrations. However, the salivary glucose levels did not consistently mirror the severity of diabetes. The study underscores the potential of SGM as a non-invasive method for diabetes detection, with the need for further research on a larger scale to establish its diagnostic value. The limitations include a small sample size and the influence of different conditions on salivary glucose composition.

Author	Study	Results
Ephraim RKD *et al.*[10] March 2019.	Patients with diabetes and those without the disease were evaluated in terms of diagnostic performance and association between salivary, serum, and capillary blood glucose.	The research was carried out at the Methodist Faith Healing Hospital in Ghana and aimed to compare the diagnostic performance of salivary glucose, serum glucose, and capillary blood glucose in diabetes and non-diabetes patients. The case-control study included 138 participants aged 30-79 years, with 79 newly diagnosed diabetic patients and 59 healthy non-diabetic controls. Salivary, serum, and capillary glucose levels were measured, and statistical analyses were performed. Results indicated significantly higher levels of fasting salivary, serum, and capillary whole blood glucose in diabetic patients compared to controls. Strong positive correlations were observed between salivary glucose and serum as well as capillary whole blood glucose. Diagnostic performance analysis showed that salivary glucose had 80.0% sensitivity and 95.0% specificity at a cutoff of ≥0.5 mmol/L for predicting diabetes, with an overall accuracy of 91.0%. While blood glucose levels demonstrated higher diagnostic accuracy, the study suggests that salivary glucose could serve as a non-invasive tool for monitoring glycemic control in type 2 diabetes if estimation methods are improved. Limitations included a small sample size and variations in glucose measurement methods that need consideration in future studies.
Naseri R *et al.*[11] Oct 2018.	Comparison of salivary glucose, IgA, total protein and amylase in individuals with T2DM to those in controls and assessed the relationship between salivary glucose levels and serum glucose and HbA_{1c} levels in both groups.	This meta-analysis included a total of 25 case-control studies analyzing various salivary parameters. The results revealed that salivary glucose levels were significantly higher in diabetic patients compared to healthy controls. Salivary total protein levels were also elevated in diabetic patients, while amylase levels were lower. Salivary secretory Immunoglobulin A (s. IgA) levels showed no significant difference between the two groups. Correlation analyses demonstrated a significant association between salivary and serum glucose levels in both groups as well as a notable correlation between salivary glucose and serum HbA_{1c} levels in diabetic patients. The study proposes a potential role for salivary tests, especially for glucose, in the diagnosis and monitoring of Type 2 Diabetes. Emphasis is placed on the importance of considering the conditions of saliva sampling, whether fasting or nonfasting, for accurate interpretation.
Tiongco RE *et al.*[12] Sep 2018	To examine whether salivary glucose can be used instead of blood glucose for the detection, diagnosis, and follow-up of T2DM.	This study assessed the potential of using saliva as a non-invasive diagnostic tool for T2DM. Involving 75 participants aged 31 to 61, the research compared salivary glucose levels across groups with Normal Fasting Glucose (NFG), Impaired Fasting Glucose (IFG), and Provisional Diabetes Mellitus (PDM). Ethical approval was obtained, and participants underwent fasting with subsequent saliva and blood sample collection. Statistical analyses, including correlation, regression, and ANOVA were conducted. The study determined a cut-off point for T2DM diagnosis using Receiver Operating Characteristic (ROC) curve analysis.
Bhattacharyya A *et al.*[35] Aug 2018.	To evaluate the relationship between blood glucose levels and salivary glucose among individuals with and without diabetes.	The study aimed to evaluate the similarity between salivary and blood glucose levels in diabetic and non-diabetic subjects as well as the similarity between salivary glucose levels and oral candidal carriage in patients with T2DM. The findings revealed a significant elevation of salivary glucose in diabetics, correlating strongly with blood glucose levels. Salivary glucose holds promise for noninvasive glycemic monitoring. Despite elevated oral candidal carriage in diabetics, the correlation with salivary glucose is weak, suggesting multifactorial influences. Further research with larger samples is needed for validation and elaboration.

Prospects

Advancements in the field of SGM hold significant promise for enhancing diabetes management. A synergistic approach combining various aspects could redefine how diabetes is monitored and addressed. This synergy has the potential to bring about significant positive changes in the way we approach and care for individuals with diabetes.

Technological Precision and Standardization

Advancements in accuracy and consistency through ongoing research and technological developments could lead to standardized testing methods and devices.[7] This prospect ensures enhanced precision and reliability in salivary glucose measurements, crucial for effective diabetes management.

Innovations Minimizing External Factors

Innovations aimed at minimizing external interference in SGM technology offer the potential for more accurate and reliable glucose readings. These developments aim to reduce the impact of external factors on saliva composition, contributing to interference-resistant and dependable SGM.

Personalized Reference Ranges

Deeper research into saliva composition variability presents the opportunity to develop personalized reference ranges. Understanding and addressing the unique variations in saliva composition could optimize the utilization of salivary glucose data for tailored diabetes management plans.

Clinical Validation and Recognition

Increased clinical validation studies could establish SGM as a recognized and accepted method in diabetes care. This recognition paves the way for the integration of SGM into routine protocols, contributing to a more comprehensive approach to diabetes management.

Seamless Integration with Existing Methods

Technological solutions facilitating seamless integration of SGM data with existing monitoring methods, including traditional approaches, offer a holistic view of diabetes management.[26] This integrated approach ensures a comprehensive understanding of a patient's health and facilitates informed decision-making.

Enhanced Affordability and Accessibility

Efforts to reduce costs and improve accessibility aim to increase the adoption of SGM technology. Particularly significant in resource-limited settings, enhanced affordability ensures that SGM becomes more widely available, benefiting individuals with diabetes globally.[4]

Patient-Centric Care and Adherence

Patient-centric approaches, including education programs and user-friendly SGM devices, are poised to improve patient adherence to monitoring routines. This prospect ensures consistent and meaningful data collection, vital for effective diabetes management and patient well-being.

CONCLUSION

The global prevalence of diabetes underscores the critical need for effective diagnostic and monitoring tools. The exploration of SGM as a non-invasive and user-friendly method offers a promising avenue for addressing this healthcare challenge. Despite facing challenges related to accuracy, external factors, and saliva composition variability, SGM presents distinct advantages in terms of comfort, convenience, and continuous monitoring. The potential future of SGM depends on several key considerations and advancements. These include technological precision to enhance accuracy, innovations to minimize external interference, the establishment of personalized reference ranges, increased clinical validation, enhanced affordability, and a shift toward patient-centric care. The similarity observed between salivary and blood glucose levels, coupled with the non-invasive and cost-effective nature of saliva-based diagnostics, adds to the reliability and feasibility of SGM.

The identification of unstimulated parotid salivary glucose before breakfast as an ideal collection method further supports the potential of saliva as a diagnostic tool for diabetes. This method could serve as a reference for predicting diabetes, providing a reliable alternative to traditional blood glucose tests. However, it is crucial to consider additional factors such as glycemic management and insulin resistance in the interpretation of salivary glucose levels. While the safety and ease of collecting saliva samples make it an attractive option, further research with a larger sample size is imperative to establish the viability of saliva as a replacement for other diagnostic fluids.

In summary, overcoming challenges and embracing potential opportunities could make SGM a valuable tool in managing diabetes. Ongoing advancements in saliva-based diagnostics align with the broader goal of improving patient care through non-invasive, accessible, and reliable monitoring of diabetes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; **GDM:** Gestational Diabetes Mellitus; **FPG:** Fasting Plasma Glucose; **OGTT:** Oral Glucose Tolerance Test; **IGT:** Impaired Glucose Tolerance**; IFG:** Impaired Fasting Glucose; **SGM:** Salivary Glucose Measurement.

SUMMARY

Diabetes is a chronic metabolic disorder characterized by hyperglycemia, resulting from defects in insulin secretion, action, or both. It poses a global health threat and is associated with various complications affecting organs such as the eyes, kidneys, heart, nerves, and blood vessels. Diagnosis relies on laboratory tests, physical examinations, and medical history assessments, with criteria including HbA_{1c} levels, fasting plasma glucose, and oral glucose tolerance tests. Early detection is crucial to prevent complications such as retinopathy and neuropathy. Prediabetes, indicating elevated diabetes risk, is linked to cardiovascular diseases and obesity. Salivary Glucose Measurement (SGM) has emerged as a non-invasive, convenient method for monitoring glucose levels, offering advantages like painless sampling, continuous monitoring potential, and reduced infection risk. However, challenges such as accuracy, external

factors' interference, and clinical validation must be addressed for effective integration into diabetes management. Prospects include technological precision, innovations minimizing external factors, personalized reference ranges, increased clinical validation, seamless integration with existing methods, enhanced affordability, and patient-centric care, offering a holistic approach to diabetes management. Further research and developments in SGM could potentially revolutionize diabetes monitoring and care.

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