

Systematic review

Salivary glucose as an alternative reliable marker in diabetes mellitus: A systematic reviewG. Anuradha¹, K. V. Swathi¹, M. Arvind²¹Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, Chennai, Tamil Nadu, India²Department of Oral Medicine and Radiology, Saveetha Dental College, Chennai, Tamil Nadu, India

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ABSTRACT

Introduction and Aim: Diabetes mellitus (DM) is a chronic metabolic endocrine condition characterised by elevated blood glucose levels that can be brought on by insulin resistance, insulin deficiency, or both. As a non-invasive diagnostic tool, saliva is a complex biological fluid that contains numerous enzymes, growth factors and microbial antibodies. The objective of this systematic review is to examine and analyse published studies that have estimated the levels of salivary glucose in people with type 1 diabetes.

Materials and Methods: MeSH terms from the electronic search database engines such as PubMed, PubMed Central, Science Direct, Cochrane Library and Google Scholar were extensively used in this search methodology in this systematic review. The precise audit has been enlisted in the PROSPERO data set (Enrolment Number: CRD42021287015). 18 articles were retrieved all together. This systematic review included two articles after the application of the inclusion and exclusion criteria.

Results: A total of 347 type 1 DM cases (174 controlled diabetics, 173 uncontrolled diabetics) and 84 controls were dissected for the appraisal of the salivary glucose levels. Using Review Manager 5.4.1, a quality assessment of the included studies produced risk of bias and applicability concern graphs.

Conclusion: The emerging field of salivary diagnostics provides real-time diagnostic values for numerous diseases. The salivary and serum glucose concentrations in Type 1 diabetes were found to be statistically correlated in the studies analysed in this systematic review, thus making them a useful monitoring tool for determination of the disease's status.

Keywords: Type 1 Diabetes Mellitus (DM); saliva; glucose; diagnosis; blood glucose.

INTRODUCTION

As per the World Health Organisation (WHO), Diabetes Mellitus (DM) in many occurrences, a sedentary lifestyle related to constant metabolic sickness portrayed by raised degrees of blood glucose that makes multi organ entanglements of the heart, veins, kidneys, nerves and eyes (1). Defective insulin action, secretion, or both lead to hyperglycemia in diabetes, a group of metabolic diseases. The International Diabetes Federation (IDF) estimates that 537 million adults worldwide (or 1 in 10) suffer from diabetes mellitus. These numbers are expected to rise to 643 million by 2020 and to 784 million by 2045. Additionally, 6.7 million people will die from diabetes in 2021, with 81% adults (or 4 in 5) living in low- and middle-income group countries (2).

The state of chronic hyperglycemia of diabetes is often linked to long-term damage, multi organ failure and dysfunction especially involving the kidneys, nerves, heart, blood vessels and eyes. The patients who are affected with DM have high probability of developing long term macro vascular and micro vascular complications like peripheral neuropathy, retinopathy, atherosclerotic disease, cerebrovascular disease etc., (3). Insulin is a peptide anabolic chemical messenger delivered by the beta cells of the islets of Langerhans cells of the pancreas. The biosynthesis and release of

insulin is governed by many factors such as alterations during the levels of gene transcription, translation or post translational modification as well as influenced by secretory granules that release insulin (4). The different types of diabetes mellitus include Type 1 diabetes mellitus, which has juvenile or childhood onset and is insulin-dependent, is one of the various forms of diabetes mellitus. The paediatric children who are impacted with Type 1 DM manifest side effects of polyuria, polydipsia and in specific cases likewise with diabetic ketoacidosis (5). Insulin resistance is primarily to blame for the non-insulin dependent or adult-onset form of diabetes mellitus. Type 2 diabetes is primarily brought on by a sedentary lifestyle that contributes to obesity as well as due to physical inactivity. As per the scientific case reports, it is said that day to day active work diminishes the gamble of fostering the adiposity incited DM as it lessens the aggregate, stomach fat and further insulin obstruction (6). According to the accelerator hypothesis, both Type 1 and Type 2 DM are the same disorder, but they can be distinguished by the measurement of three accelerators- insulin resistance, beta cell death and beta cell immunity (7), a hybrid variety of diabetes has symptoms that combine those of both types. The gestational form of diabetes, which affects pregnant women, is the third type of diabetes. It is characterised by hyperglycemia, with elevated

blood glucose levels that are still within the DM diagnostic reference range. Because these women are at high risk of developing type 2 diabetes in the future, they should have their glucose levels checked promptly six to twelve weeks after giving birth and periodically once every three years thereafter (8). If the glucose intolerance persists after the sixth to seventh week of pregnancy, a diagnosis of gestational diabetes is made (9). DM can also be caused by other etiological factors, such as monogenic diabetes syndromes like neonatal diabetes or young adult maturity-onset diabetes, diseases of the exocrine glands like pancreatitis or cystic fibrosis, certain drugs like glucocorticoids or HIV regimen and organ transplants (10).

The plasma glucose criteria which include fasting plasma glucose, the oral glucose tolerance test two hours after food intake and the three-month glycated haemoglobin HbA1c criteria can serve as the foundation for the diagnosis of diabetes. A condition known as prediabetes, which is an intermediate stage of hyperglycemia in which glucose levels are above the normal range but below the DM threshold, is on the rise, according to the current trend (11). There are also studies in literature where they have done metagenome analysis in buccal mucosal films for bacterial identification in patients affected with diabetes mellitus (12).

A glycated haemoglobin test known as HbA1c test is a proportion of the typical blood glucose level over a time of 2-3 months (13). According to the Centers (CDC) for Disease Control & Prevention, when the result of the HbA1c test is considered normal when the result is below 5.7%, prediabetes when it is between 5.7 to 6.4 % indicates prediabetes and definitive diabetes when it is 6.5% or higher.

In DM the micro vascular changes that occur as a result of persistent hyperglycemia that is the cause for the increased production of Advanced Glycosylation End Products (AGEs). These products will cross link with certain extracellular matrix proteins and collagen that causes alteration in the basement membrane leading to endothelial dysfunction. These AGEs can also react with their localised receptors on the plasma membrane (RAGEs) that causes alteration of the intracellular signalling pathway, certain gene expression along with the release of the highly reactive free radicals and pro-inflammatory molecules (14).

Saliva is a very valuable diagnostic tool as the collection of salivary samples is relatively easy. As saliva contains various biomarkers, it has been used in many multiplexed biochemical assays that serve as point of care diagnostic devices. The salivary biomarkers include specific markers such as immunoglobulins (particularly secretory IgA), salivary enzymes such as amylase, lysozyme, peroxidase, calcium ions, non-specific markers including proteins like mucins, lactoferrin, histatin,

cystatin, amino acids, growth factors etc., (15). It also offers real time diagnostic values and is less technique sensitive. It has been used to diagnose a variety of autoimmune conditions, including Sjogren's syndrome and cystic fibrosis, as well as significant systemic conditions like cardiovascular disease, diabetes and HIV. With regards to oral diseases, it has been implicated as a diagnostic tool for periodontitis, dental caries and oral cancer. As glucose molecules can diffuse through a membrane that is only partially permeable, salivary samples can be used to measure glucose levels. In literature, there are several studies that have shown how salivary glucose is a very potentially reliable marker for the diagnosis of type 1 diabetes mellitus in individuals. Studies in the literature have demonstrated that salivary glucose can be a reliable diagnostic marker for type 1 diabetes mellitus (16). A few studies did not show statistically significant differences in the levels of salivary glucose in this regard, but there are studies that have shown higher concentrations of salivary glucose in unstimulated saliva in comparison to stimulated saliva (17). This systematic review will investigate the new examinations that have evaluated the degrees of salivary glucose in type 1 DM patients with their serum glucose levels as the reference standard.

Research question

The research question was formulated by using the PICO format. The research question of this systematic review was formulated as 'Can patients with Type 1 diabetes mellitus monitor their glucose levels with saliva as a diagnostic tool?'

The following is the PICO of the research question:

P- Patients with Type 1 Diabetes Mellitus (DM); I- Saliva; C- Serum; O- Glucose levels.

METHODOLOGY

Search strategy for the identification of studies according to selection criteria

The Cochrane guidelines for systematic reviews were followed by the search strategy. From various search databases like PubMed, PubMed Central, ScienceDirect and Cochrane Library, articles that were relevant to the search were identified. The timeline of the article search included only studies published in the recent 5 years. The article search included only those articles that were published in English literature. The initial screening of the articles was done based at their title level following which similar duplicates were removed from the other search engines. The title of the articles and abstracts were initially screened and analysed. The full text of the selected articles was retrieved and a further complete analysis was done according to the selection criteria for their inclusion into the systematic review.

Search methodology

The search methodology was carried out in PubMed database by using the following keywords: (saliva) OR (salivary) AND (Glucose) OR (D-Glucose) OR (D Glucose) OR (Dextrose)) OR (Glucose, (alpha-D)-Isomer) OR (Anhydrous Dextrose) OR (Dextrose, Anhydrous) OR (Glucose, (DL)-Isomer) OR (Glucose, (L)-Isomer)) OR (L-Glucose)) OR (L Glucose) OR (Glucose Monohydrate)) OR (Monohydrate, Glucose)) OR (Glucose, (beta-D)-Isomer) AND (Serum) OR (Blood Serum) OR (Serum, Blood) AND (Diabetes Mellitus, Insulin-Dependent) OR (Diabetes Mellitus, Insulin Dependent) OR (Insulin-Dependent Diabetes Mellitus) OR (Diabetes Mellitus, Juvenile-Onset) OR (Diabetes Mellitus, Juvenile Onset) OR (Juvenile-Onset Diabetes Mellitus) OR (IDDM) OR (Juvenile-Onset Diabetes) OR (Diabetes, Juvenile-Onset) OR (Juvenile Onset Diabetes) OR (Diabetes Mellitus, Sudden-Onset) OR (Diabetes Mellitus, Sudden Onset)) OR (Sudden-Onset Diabetes Mellitus)) OR (Type 1 Diabetes Mellitus)) OR (Diabetes Mellitus, Insulin-Dependent, 1)) OR (Insulin-Dependent Diabetes Mellitus 1)) OR (Insulin Dependent Diabetes Mellitus 1)) OR (Type 1 Diabetes)) OR (Diabetes, Type 1)) OR (Diabetes Mellitus, Type I)) OR (Diabetes, Autoimmune)) OR (Autoimmune Diabetes)) OR (Diabetes Mellitus, Brittle)) OR (Brittle Diabetes Mellitus)) OR (Diabetes Mellitus, Ketosis-Prone)) OR (Diabetes Mellitus, Ketosis Prone)) OR (Ketosis-Prone Diabetes Mellitus))

Registration

The International Prospective Register of Systematic Reviews (PROSPERO) Database has received this systematic review's registration. (Registration Number: CRD42021287015).

Criteria for study selection

The search dates for the relevant studies were from 2017 to 2021. Studies published only in English language and human studies only have been included. The searches were evaluated prior to the final analysis. Unpublished studies from grey literature will not be sought. The selection criteria where patients with type 1 DM were included. Patients with other types of diabetes, including gestational diabetes and Type 2 diabetes, those taking medications that alter salivary flow, patients with other medically compromised conditions apart from type 1 DM, on radiotherapy or chemotherapy for any malignancies and those with salivary gland diseases or underwent previous surgeries were excluded from the review.

This systematic review examines studies that evaluated Type 1 DM patients' glucose levels using saliva. Because glucose molecules can easily diffuse through a semipermeable membrane, it is possible to measure elevated glucose levels in diabetic patients by collecting salivary samples using either unstimulated

or stimulated methods for routine monitoring and prognosis.

The comparator of the included studies was serum which is usually extracted from the blood and glucose is measured in the serum.

The search yielded case control studies which have evaluated the effectiveness of glucose to monitor patients with type 1 DM. (It will be screened and included after proper evaluation by all the reviewers) Estimation of glucose levels is the main outcome of this systematic review. The glucose levels estimated in saliva by unstimulated or stimulated methods can be a marker for checking the variations in diabetes mellitus patients for monitoring the disease levels.

Study synthesis

This systematic review included 3 reviewers for application of the eligibility criteria and selection of studies for inclusion in the systematic review (one person will screen and others will check decisions). Any disagreements between individual judgements were resolved by repeating the search strategy again at the initial phase itself. Review Manager 5.4.1 software was used for decision making.

Data extraction

Studies which have included type 1 diabetes mellitus patients (baseline demographic characteristics-such as age, gender, associated comorbidities, medication history) were extracted. 3 reviewers checked the received data (*i.e.*, One person was involved independently for the data extraction and two persons were involved to check the extracted data). The disagreements between individual judgements were resolved at each phase of the systematic review starting from search strategy till the finalisation process of the manuscript. Data was recorded using Review Manager 5.4.1 (For quality assessment of included studies) was used to record the data for the patient selection, index test, reference standard, flow and timing and risk of bias evaluations. Consequences of the appraisal were utilized to characterize the attributes of the relative multitude of remembered examinations for the efficient audit. One person was used to review the entire circle and two reviewers were involved in the quality assessment. During the process of selecting the study and extracting the data, disagreements that existed between the individual reviewers were resolved. Information blend and quality appraisal of the examinations were finished utilizing programming software (Review Manager 5.4.1) and scientific evidence assessment with Oxford's level of evidence.

RESULTS

Literature evaluation

This systematic review included two studies in total (Fig. 1) and were thoroughly examined (Table 1). The

study group (controlled diabetics) and the total number of samples analysed for the estimation of salivary glucose in Type 1 DM include 80 % of diabetics of which the controlled and uncontrolled population equally distributed to 40% and healthy control subjects who accounted to 20% of the population.

Quality assessment of the studies

The QUADAS tool 2 was used to evaluate the quality of the two included studies. There are typically four domains for quality assessment of diagnostic accuracy studies: patient sampling, index test, reference

standard, flow and timing. Each one of these domains had two to four enquiries which had to be addressed as 'yes', 'no' or 'unclear'. The information was taken into the Review Manager 5.4.1 software to get a variety of coded outline of hazard of predisposition and relevance concern (Fig. 2).

Risk of bias and applicability concern

Both the studies, Bhattacharya *et al.*, (18) and Kartheeki *et al.*, (19) had a low risk with regards to their applicability concern and were unclear with regards to risk of bias (Fig 3).

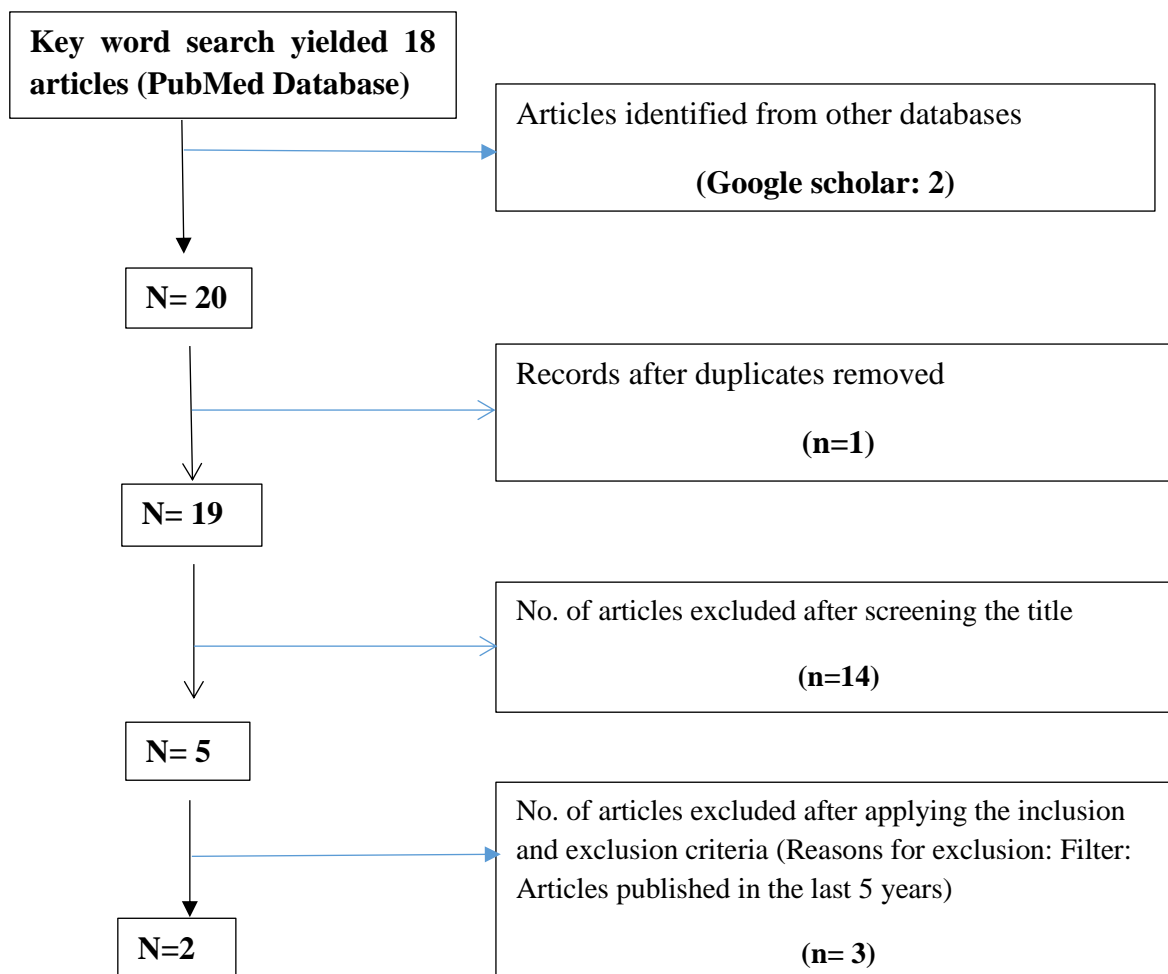


Fig. 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) flow chart

Table 1: The characteristics of the included studies

Author, Year of Publication, Journal and Country	Design of the study and Evidence Level	Sample distribution	Methodology Sample collection (Saliva)	Methodology Sample collection (Serum)	Estimation of glucose from samples	Results	Inferences
Bhattacharya et al. 2016, Journal of Oral Biology and craniofacial Research, India	Case-Control Study (3 b)	Group 1: Control (n=34) Group 2 a: Controlled diabetics (n=49) Group 2 b: Uncontrolled diabetics (n=48)	2 ml of two unstimulated salivary samples were collected (Fasting samples- overnight 8 hour fasting and collected in the morning Postprandial samples- Taken	2 ml of serum was collected from the median cubital vein by intravenous method.	For two minutes, the serum and salivary samples were centrifuged at 2000 rpm. The salivary glucose levels were measured by Glucose	Mean fasting salivary glucose levels: Group 1: 7.18 mg/dl Group 2: 9.14 mg/dl Group 3: 15.21 mg/dl	There was a statistically significant high correlation in salivary and serum glucose levels with regard to both diabetic as well as non-

			1.5-2 hours post meal) It was collected in a sterile graduated tube that contained sodium fluoride and Ethylenediamine tetra acetic acid (EDTA) by spitting method for 5 minutes and was processed immediately.		Oxidase Peroxidase technique. Utilized semi-auto analyser: Ten microliters of samples and 500 microliters of glucose were added to the Microlab 300, Merck & Co. Inc., USA Incubation temperature: 37 degrees Incubation time: 15 minutes	Mean postprandial salivary glucose levels: Group 1: 10.731 mg/dl Group 2: 12.379 mg/dl Group 3: 21.831 mg/dl Mean fasting blood glucose levels: Group 1: 92.51 mg/dl Group 2: 96.62 mg/dl Group 3: 170.76 mg/dl Mean postprandial blood glucose levels: Group 1: 137.15 mg/dl Group 2: 142.63 mg/dl Group 3: 266.40 mg/dl	diabetic individuals.
Kartheeki et al. 2017, International Journal of Clinicopathological Correlation, India	Case-control study (3b)	Group 1: Control (n=50), Group 2: Controlled diabetics (n=125). Group 3: Uncontrolled diabetics (n=125)	By spitting for 10 minutes, 2 millilitres of unstimulated saliva were collected in sterile graduated tube post overnight fasting.	2 ml of entire blood was collected by the utilization of a 24-gauge sterile syringe from the ante cubital fossa while the subjects were made to be in resting position	For 20 minutes, the samples were centrifuged at 3000 rpm. The glucose reagent was mixed with 100 microliters of the test sample at 37 degrees. Incubation time: 5 minutes Semi-automated analyser was used: Erba Chem 7	Salivary glucose levels: Group 1: 1.2 mg/dl Group 2: 2.48 mg/dl Group 3: 3.37 mg/dl Serum glucose: Group 1: 99.58 mg/dl Group 2: 171.10 mg/dl Group 3: 352.61 mg/dl	There was significant correlation between salivary and serum glucose levels despite the fact salivary glucose levels varied from serum glucose levels.

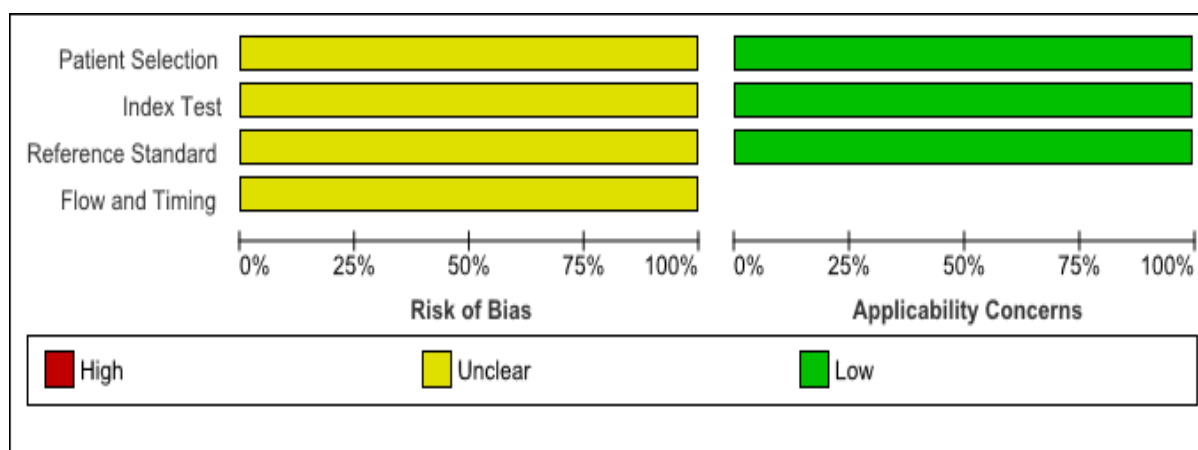


Fig. 2: Concerns regarding applicability and risk of bias graph; assessment of each domain by review authors, expressed as percentages across included studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Bhattacharya et al. 2016	?	?	?	?	+	+	+
Kartheeki et al. 2017	?	?	?	?	+	+	+
<div> ● High ● ? Unclear ● + Low </div>							

Fig. 3: Chance of predisposition and appropriateness concerns outline: survey authors' decisions about every space regarding the included studies

DISCUSSION

Diabetes mellitus is a metabolic condition characterized primarily by an abnormal rise in blood glucose levels. This metabolic disease, which is caused by a sedentary lifestyle, has a high morbidity and mortality rate and is linked to infections that can affect multiple organs. It could be a problem for society. To avoid these long-term problems, it's critical for people to be diagnosed with diabetes as soon as possible and to be closely monitored for their condition. When it comes to screening, monitoring, and diagnosing diabetes mellitus, also known as a continuous evaluation of the disease's status, a serum blood test is always regarded as the gold standard. The invasive nature of serological testing, anxiety concerns, and the fact that it can increase the risk of developing finger calluses, peripheral neuropathy, and infection in long-term diabetics are some of the challenges associated with it. The neurological, hormonal, nutritional, and metabolic states of an individual influence the composition of saliva, a complex biological fluid. In diabetic patients, salivary glucose appears to be a reliable method for evaluating serum glucose concentrations.

Because it is a small molecule, glucose easily diffuses through a membrane that is only partially permeable. Whenever there is a sudden spike in serum glucose levels, the centralization of glucose in saliva is additionally expanded. This increased transport of glucose from blood into saliva is caused by changes in the basement membrane of blood vessels (20). The salivary organs go about as channels of blood glucose that are affected by the hormonal or neural mechanisms. The glucose molecules in the saliva can be detected and evaluated through the gingival crevicular fluid (GCF). Concerning the relationship of salivary glucose values with blood glucose values in fasting and postprandial qualities in DM, it was found to be statistically significant in various studies across the literature. Patients with DM have higher salivary

glucose levels than non-diabetic control groups, according to numerous studies. However, this finding still remains debatable when compared to other studies in literature that had no significant differences or were just identified in diabetic patients who had poor metabolic control (23). In non-diabetics, the correlation between salivary glucose and blood variable parameters like glycemia and HbA1c was evaluated, and the results were found to be inconsistent. On the other hand, few other studies showed a strong correlation with HbA1c and glycemia (24), despite the lack of a clear correlation in some of them. Some studies showed a strong to moderate correlation between salivary glucose and glycemia (25), while others showed only a weak correlation (26).

The greater correlation between salivary glucose levels and serum glucose levels is largely attributable to the length of time that glucose takes to enter the salivary glands. A comparative report in the scientific forum with five arrangements of tests gatherings and various techniques for examination of the glucose levels in the blood and saliva detailed that the salivary glucose concentration expanded as blood glucose levels increased, typically in individuals when there was a correlation among unstimulated and invigorated salivation. It was likewise observed that there was a decrease in salivary glucose concentration, increase in the salivary stream in unstimulated saliva while there was an unaltered glucose discharge rate in stimulated saliva. However, both stimulated, unstimulated salivary glucose concentration and glucose excretion rate remained unaltered in the diabetic study group. In diabetics, there was also no statistically significant correlation between glycemia and either the rate of glucose excretion or glucose concentration, regardless of whether the saliva was stimulated or not (27). When salivary and serum glucose levels are compared, salivary glucose estimation using parotid saliva yields

a good correlation with both statistically significant results (28).

With reference to a diagnostic accuracy study by Smriti *et al.*, for the comparison of salivary glucose values in DM patients, they found to have 99.1% sensitivity and 93.7% specificity (29). The literature also uncovers one more study by Tiongco *et al.*, that demonstrated a sensitivity of 76.0% and a specificity of 90% (30). There are a number of additional studies in the literature that demonstrate the cut-off values of salivary glucose in unstimulated whole saliva samples taken during fasting. Smriti *et al.* state that if the patient's glucose levels in their saliva are higher than 7.05 mg/dL, it may be determined that they have poorly controlled diabetes mellitus. In the study of Tiongco *et al.*, the subjects who were on a fast demonstrated that blood glucose levels in their saliva that were higher than 13.22 mg/dL were indicative of diabetes. The whole, unstimulated saliva was taken, and a person was said to have diabetes if their salivary glucose level was higher than 11.60 mg/dL. Ephraim *et al.*, study derived the cut-off values for fasting capillary whole blood glucose, fasting serum glucose, and fasting salivary glucose on 79 newly diagnosed diabetic patients. At the cut-off estimates, 76.8 mmol/L for fasting salivary glucose, a sensitivity of 99% and specificity of 100.0% and the receiver operating characteristics curve (AUC) of 98.8% was noticed for foreseeing DM while a sensitivity of 80%, specificity of 95% and AUC of 91.0% was noticed for fasting salivary glucose at a fasting salivary glucose cut off value of 70.5 mmol/L. Furthermore, a cut off value of more than 6.9 mmol/L was determined for fasting capillary entire blood glucose with a 100 % diagnostic accuracy of both the sensitivity and specificity values (31).

CONCLUSION

Salivaomics is a very valuable, emerging field as the biomarkers detected in saliva can play a pivotal role in reflecting the underlying systemic disorders in a very easy, non-invasive rapid method which is often a major limitation in serum-based diagnostics. Future trends hold scope for salivary diagnostics to even replace the invasive serological testing for screening and surveillance of various systemic diseases and large scale multi centric studies with precise validation and generalizability are needed to be conducted towards this perspective.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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