Innovations

Assessment of the levels of salivary glucose in type 2 Diabetes Mellitus patients: A Systematic Review

1. G. Anuradha
Professor and Head,
Department of Oral Medicine and Radiology,
SRM Dental College, Ramapuram, Chennai.

2. K.V.Swathi
Lecturer,
Department of Oral Medicine and Radiology,
SRM Dental College, Ramapuram, Chennai.

3. M. Arvind
Professor and Academic Head,
Department of Oral Medicine and Radiology,
Saveetha Institute of Medical and Technical Sciences, Chennai.

Corresponding author: **Dr G. Anuradha**, **anug77@yahoo.com**
Received: 16 April 2022 **Accepted:** 20 May 2022 **Published:** 15 June 2022

Abstract : Background: *Diabetes mellitus (DM) is a chronic metabolic disease characterised by elevated levels of blood glucose that can occur as a result of deficiency of insulin or resistance to insulin or both. Insulin is a peptide anabolic hormone that is secreted by the beta cells of the islets of Langerhans of the pancreas. Insulin acts by enhancing glucose uptake by cells in response to elevated blood glucose levels and when blood glucose levels are low, the adjacent alpha cells secrete glucagon thus maintaining the normal glucose homeostasis. Diabetes mellitus can be Type 1 DM which is insulin-dependent or juvenile onset characterised by deficiency in insulin production, Type 2 DM which is non-insulin dependent characterised by insulin resistance and the other category known as gestational DM seen during pregnancy. Saliva is a complex fluid containing many enzymes, growth factors, microbial antibodies and it serves as a non-invasive diagnostic tool. Glucose molecules have the property to diffuse through a semipermeable membrane and they can transfer through salivary gland epithelium. Hence salivary glucose estimation can be a monitoring tool in diabetic patients.* ***Aim :*** *This systematic review aims to explore studies in literature that have estimated the levels of salivary glucose in type 2 diabetes mellitus.* ***Materials and methods :*** *The search was done using MeSH terms in the electronic databases namely PubMed, PubMed Central, Science Direct, Cochrane Library and Google Scholar. The systematic review has been registered in PROSPERO database* ***(Registration Number: CRD42021287015).*** *A total of 18 articles were retrieved. On application of the inclusion and exclusion criteria, 2 articles were included in this systematic review.* ***Results :*** *A total of 84 controls (non-diabetics), 347 cases (Type 2 DM: 174 controlled diabetics, 173 uncontrolled diabetics) were analysed for the assessment of salivary glucose levels. Quality assessment of the included studies was done using Review Manager 5.4.1 which generated risk of bias and applicability concern graphs. Both the studies, Bhattacharya et al. (2016) and Kartheeki et al. (2017) were unclear in their risk of bias and had a low risk with regards to their applicability concern.* ***Conclusion :*** *Salivary diagnostics is an emerging field and offers real time diagnostic values in many diseases. The greatest advantage is that it offers an easy, non-invasive*

collection methodology compared to serum. The studies analysed in this systematic review had a statistically significant correlation of the salivary and serum glucose concentrations in Type 2 DM and thus can be used effectively as a monitoring tool to assess the disease status.

Key words: 1.*Type 2 Diabetes Mellitus, 2.Saliva, 3.Serum, 4.Glucose*

1. Introduction

1.1 Background

According to the World Health Organisation (WHO), Diabetes Mellitus (DM) is a chronic, metabolic disease characterised by elevated levels of blood glucose that causes potential complications to the heart, blood vessels, eyes, kidneys and nerves.[1] Diabetes is a group of metabolic diseases characterised by hyperglycemia as a result of defects from insulin secretion, insulin action or both. According to the International Diabetes Federation (IDF), globally 537 million adults (1 in 10) are estimated to be living with DM and the figures have been predicted to rise to 643 million by 2020 and 784 million by 2045. 81% adults (4 in 5) affected with diabetes are in low and middle income group countries and is responsible for 6.7 million deaths in 2021 i.e. 1 in every 5 seconds. [2]

The chronic hyperglycemia of diabetes is often linked to long-term damage, dysfunction, and failure of multiple organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The patient affect with DM have the risk of developing long term micro vascular and macro vascular complications such as retinopathy, peripheral neuropathy, atherosclerotic disease, cerebrovascular disease etc. [3]Insulin is a peptide anabolic hormone produced 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 includes Type 1 DM also known as insulin-dependent, juvenile or childhood onset characterised by deficiency in insulin production in the beta cells of the islets of Langerhans in the pancreas. The children affected with Type 1 DM present with symptoms of polyuria, polydipsia and in certain cases with diabetic ketoacidosis.[5] The second type of DM is the non-insulin dependent or adult-onset that occurs due to insulin resistance. Type 2 DM mainly occurs as a result of obesity and lack of physical activity. According to literature, it is said that regular physical activity reduces the risk of developing adiposity induced DM by causing the reduction of the total and abdominal fat and improves the insulin resistance. [6] A combination of the symptoms of both type 1 and type 2 DM has been identified as hybrid variety of DM attributed due to accelerator hypothesis which state that both Type 1 and Type 2 DM are the same disorder but can be distinguished by the measurement of three accelerators that include beta cell death, insulin resistance and beta cell immunity. [7]The third category is gestational DM that is seen in pregnancy and is characterised by hyperglycaemia with elevated blood glucose levels but below the diagnostic reference range for DM. These women are at a risk of developing type 2 DM in the future. These women should be screened 6-12 weeks postpartum for the glucose levels and once in three years subsequently for development of diabetes.[8]A diagnosis of gestational DM is given if there is glucose intolerance beyond 6 to 7 weeks of gestation.[9]DM can also occur due to certain other causes such as monogenic diabetes syndromes such as neonatal diabetes, maturity onset diabetes of the young or due to diseases of the exocrine glands such as pancreatitis, cystic fibrosis or due to certain drugs such as glucocorticoids, or HIV regimen or due to organ transplantation. [10]

The diagnosis of DM can be based on plasma glucose criteria that are by fasting plasma glucose or 2 hours after intake of food during oral glucose tolerance test or by HbA1c criteria. A condition known as prediabetes can occur which is an intermediate stage of hyperglycemia where the glucose levels are above the normal range but below the threshold level for DM. [11]

A glycated haemoglobin test known as HbA1c test measures the average blood glucose level for the past 2-3 months. [12] According to the CDC, an HbA1c test result of below 5.7% is considered as normal, 5.7 to 6.4 % indicates prediabetes and a value of 6.5% or more indicates a definitive DM.

In DM the micro vascular changes that occur as a result of persistent hyperglycemia which leads to 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, gene expression with release of free radicals and pro inflammatory molecules.[13]

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. [14] It also offers real time diagnostic values and is less technique sensitive. It has many immense applications and has been used in the diagnosis of various autoimmune disorders like Sjogren's syndrome, cystic fibrosis and other systemic disorders such as cardiovascular disorders, diabetes mellitus, HIV. With regards to oral diseases, it has been implicated as a diagnostic tool for periodontitis, dental caries and oral cancer. [15]Glucose molecules have the property to diffuse through the semipermeable membrane and can be measured by the collection of salivary samples. According to literature, there are studies that revealed the concentrations of salivary glucose were higher in unstimulated saliva in comparison to stimulated saliva, though few studies did not show significant differences in the salivary glucose levels in this regard. [16]This systematic review will explore the recent studies that have assessed the salivary glucose levels in type 2 DM patients with their serum glucose levels as the reference standard.

1.2 Research question

The research question was formulated by using the PICO format.
The research question of this systematic review was formulated as "Can saliva be used as a diagnostic tool to monitor the glucose levels in patients with Type 1 Diabetes Mellitus"?
The PICO of the research question is as follows:
P- Patients with type 2 diabetes mellitus
I-Saliva
C- Serum
O- Glucose levels

2. Methodology

2.1 Search strategy for identification of studies

The search strategy was done according to the Cochrane guidelines for systematic reviews. Articles relevant to the search strategy were identified from search data bases of PubMed PubMed Central, ScienceDirect, Cochrane Library and Google Scholar. The timeline of the article search included only studies published in the last 5 years. The article search included only those published in English literature. The initial screening of the articles were done based on their titles following which similar duplicates were removed from the other databases. The title of the articles and abstracts were initially

screened and analysed. The full text of the selected articles were retrieved and further analysis was done for their inclusion into the systematic review.

2.2 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)

2.3. Registration

This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) Database. (Registration Number: **CRD42021287015**)

2.4 Study selection criteria

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 will be re-run prior to the final analysis. Unpublished studies from grey literature will not be sought. The selection criteria was patients with type 2 DM were included. Patients with other types of DM (Such as Type 1 DM, Gestational DM), those on drugs that alteration in salivary flow, patients with other medically compromised conditions apart from type 2 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 analyses studies that have used saliva in the assessment of the glucose levels in Type 2 DM patients. Glucose molecules have the ability to readily diffuse through the semipermeable membrane, hence in diabetic patients as glucose levels are elevated it can be assessed by the collection of salivary samples either by unstimulated or stimulated methods for routine monitoring and prognosis of the condition.

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 2 DM. (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 are 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.

2.5 Study synthesis

This systematic review included 3 reviewers for applying the eligibility criteria and selecting 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.

2.6 Data extraction

Studies which have included type 2 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). Disagreements between individual judgements were resolved at each phase of the review starting from search strategy till manuscript completion. Data was recorded using Review Manager 5.4.1 (For quality assessment of included studies) for assessing patient selection, index test, reference standard, flow and timing and for risk of bias. Results of the assessment was used to define the characteristics of all the included studies. 2 reviewers were involved in the quality assessment and 1 person was used to check the overall article. Disagreements between reviewers were resolved while doing the study selection and data extraction process. Data synthesis and quality assessment was done using software (Review Manager 5.4.1) and assessment with Oxford's level of evidence.

3. Results

3.1 Literature evaluation

A total of two studies were included in this systematic review (Fig 1) and were analysed in detail (Table 1). The total number of samples analysed for the estimation of salivary glucose in Type 2 DM includes Study group (Controlled Diabetics: 40%, Uncontrolled Diabetics: 40%) and Controlled group (20%).

3.2 Quality assessment of the studies

The quality assessment of both the included studies were assessed by QUADAS tool 2. Quality assessment of diagnostic accuracy studies has four domains namely patient sampling, index test, reference standard, flow and timing. Each of these domain had two to four questions which were answered as “yes”, “no” or “unclear”. The data was fed into the Review Manager 5.4.1 software to obtain a colour coded chart of risk of bias and applicability concern. (Fig 2)

3.3 Risk of bias and applicability concern

Both the studies, Bhattacharya et al. [17](2016) and Kartheeki et al.[18] (2017) were unclear in their risk of bias and had a low risk with regards to their applicability concern. (Fig 3)

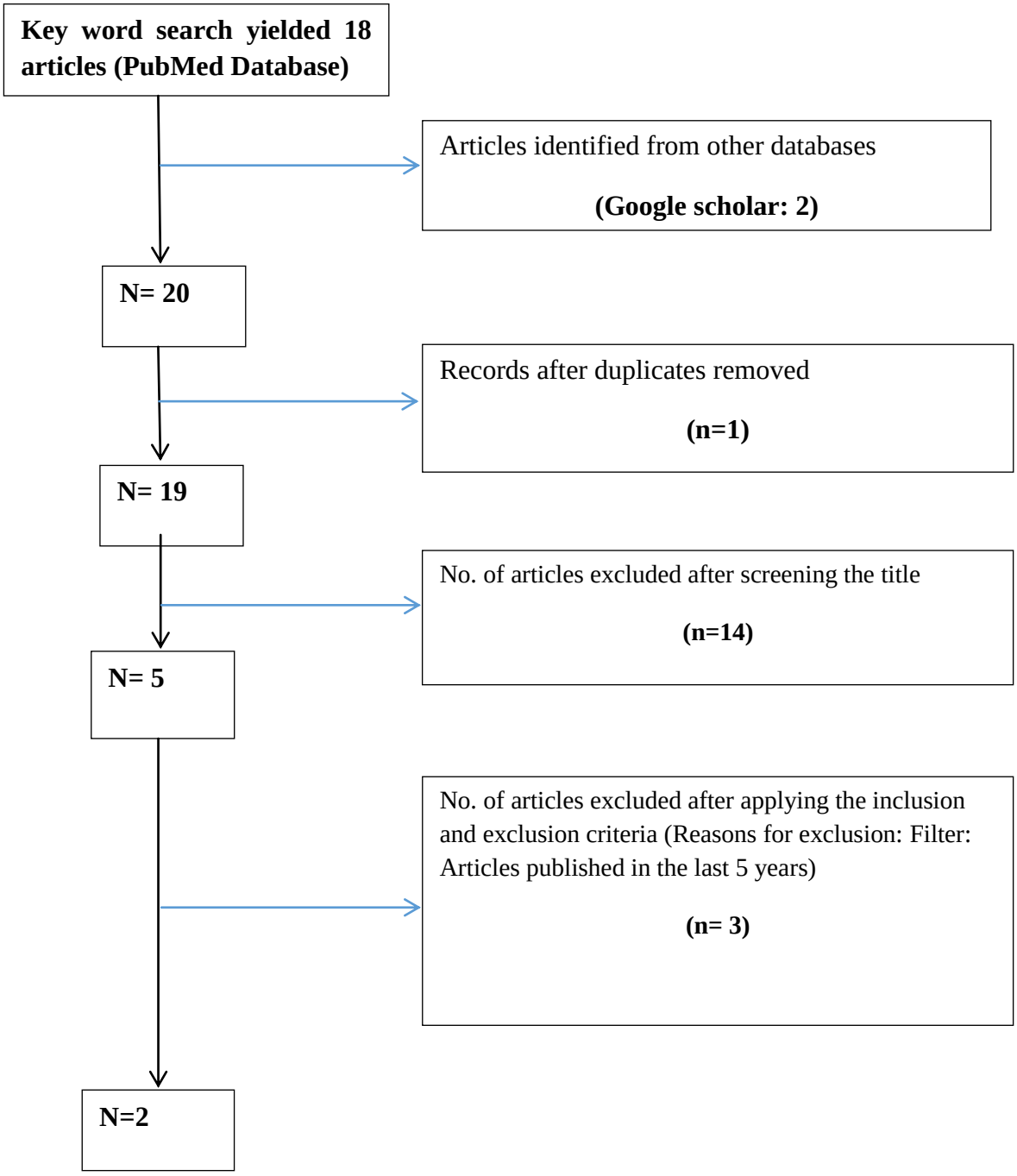

Fig 1: PRISMA flow diagram

Table 1: Characteristics of included studies

Author, Journal, Year and country	Study Design and Level of Evidence	Sample distribution	Methodology Sample collection(Saliva)	Methodology Sample collection(Serum)	Analysis of samples for glucose estimation	Results	Inferences
Bhattacharya et al. 2016, Journal of Oral Biology and craniofacial Research, India	Case-Control Study (3b)	Group 1: Control (N=34) Group 2a: Controlled diabetics (N=49) Group 2b: Uncontrolled diabetics (N=48)	2ml of two unstimulated salivary samples were collected (Fasting samples- overnight 8 hour fasting and collected in the morning Post prandial samples- Taken 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.	2ml of blood was collected from the median cubital vein by intravenous method.	Both the salivary and serum samples were centrifuged at 2000 rpm for 2 minutes. The salivary glucose levels was assayed by Glucose Oxidase Peroxidase method. Semi autoanalyser used: Microlab 300, Merck & Co. Inc., USA 10 microlitres of samples were added with 500 microlitres of glucose reagent Incubation temperature: 37 degrees Incubation time: 15 minutes	Mean fasting salivary glucose levels: Group 1: 7.18 mg/dl Group 2: 9.14 mg/dl Group 3: 15.21 mg/dl Mean post prandial 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 post prandial blood glucose levels: Group 1: 137.15 mg/dl Group 2: 142.63 mg/dl Group 3: 266.40 mg/dl	There was a high correlation with salivary and serum glucose levels in both diabetics as well as non-diabetics.

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)	2 ml of fasting unstimulated saliva was collected in a sterile graduated tube by spitting method for 10 minutes.	2 ml of whole blood was collected by using a 24 gauge needle sterile syringe from the ante cubital fossa while the subjects were in resting position	Samples were centrifuged at 3000 rpm for 20 minutes. 100 microlitres of test sample was mixed with glucose reagent. Incubation temperature: 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	Salivary glucose levels had variations I proportions to serum glucose levels and there was significant correlation between salivary and serum glucose levels.

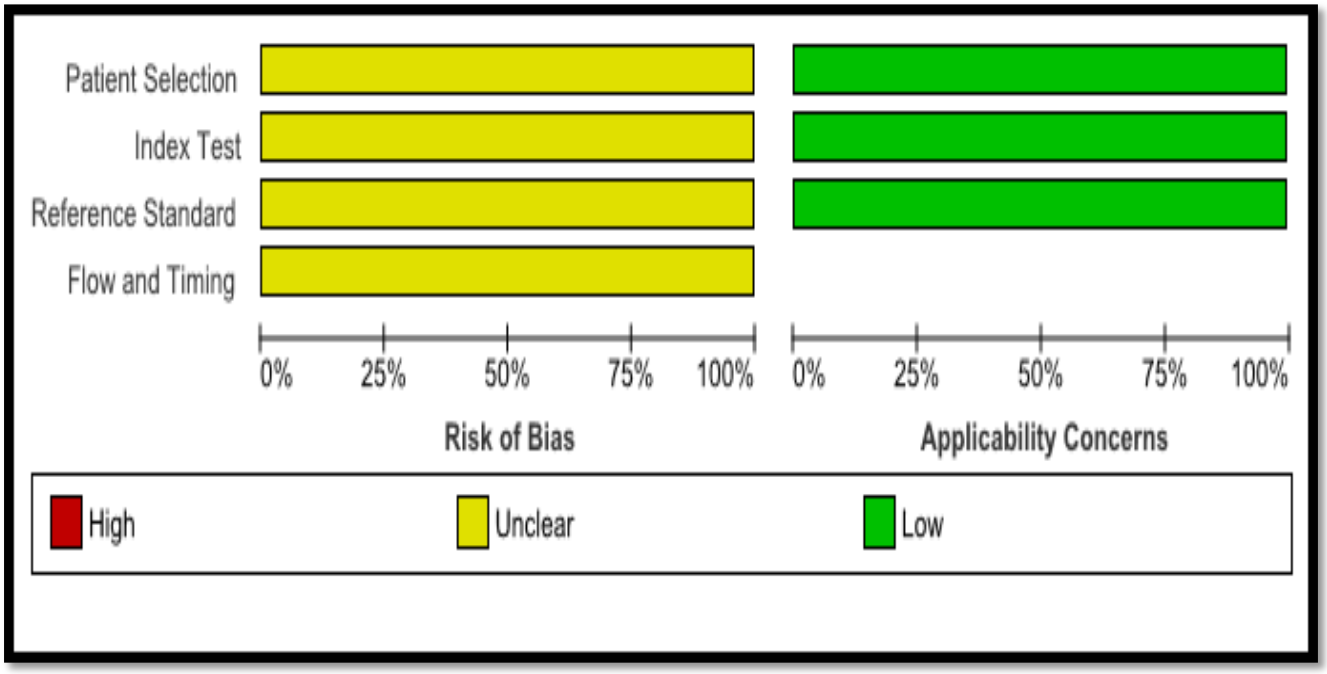

Fig 2: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

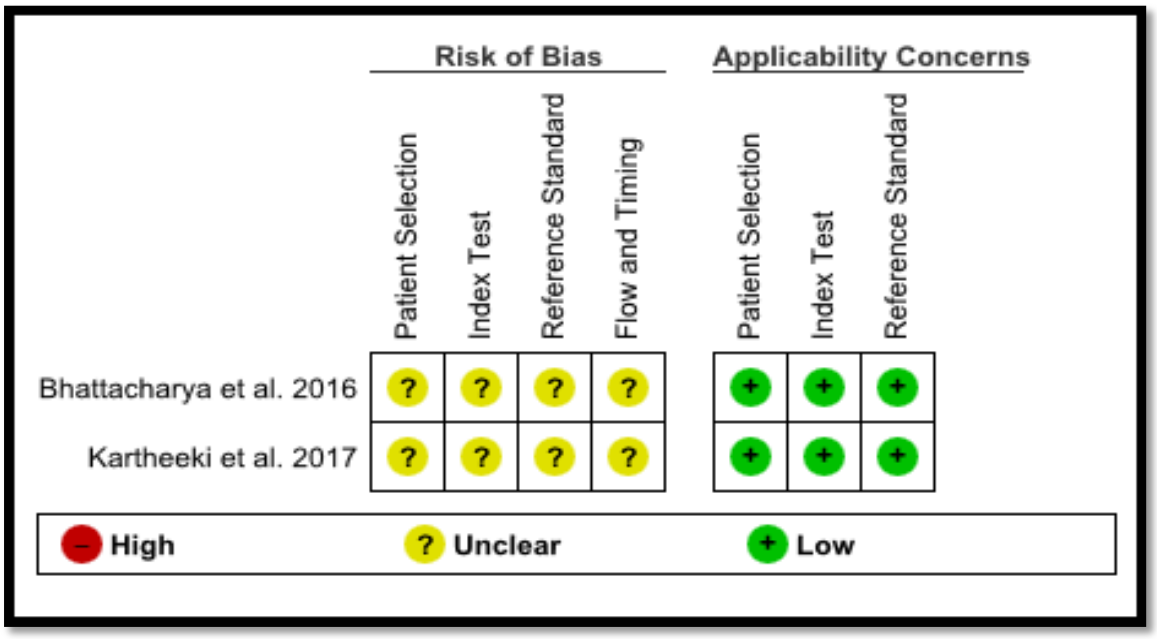

Fig 3: Risk of bias and applicability concerns summary: review authors' judgements about each domain for the included studies

Discussion

Diabetes mellitus is a metabolic disease characterised by abnormally elevated blood glucose levels. This metabolic disease is a potential burden in the society due to its high morbidity and mortality associated with infections and its complications in various systems. So, an early detection and monitoring of diabetic status in individuals is very essential. Blood testing is the gold standard test for screening, monitoring and diagnosing diabetes despite being invasive and painful. The challenges in serological testing can be attributed to its invasiveness, anxiety concerns and in long term diabetes, it can increase the risk of development of finger calluses, poor peripheral circulation and risk of infection. Salivary glucose appears to be a reliable indicator of serum glucose concentrations in diabetes. Saliva is a biological fluid that reflects local and systemic changes because the composition of saliva is influenced by hormonal, neurologic, nutritional and metabolic state of an individual.

Glucose is a small molecule and it easily diffuses through the semi permeable membrane. When there is elevation of serum glucose levels, the concentration of glucose in saliva is also increased. The alterations in the basement membrane of blood vessels leads to increased transport of glucose from blood into saliva. [19]The salivary glands act as filters of blood glucose that would be altered by hormonal or neural regulation. Glucose can also be present in saliva through gingival crevicular fluid. [20] With regards to the correlation of salivary glucose values with blood glucose values in fasting and post prandial values in Type 2 DM, it was found to be significant in various studies in the literature. Many studies show an increase in salivary glucose levels in type 2 DM compared to non-diabetic controls. [21] However, this finding remains controversial as in other studies, no significant differences were detected or only detected in DM who had poor metabolic control.[22] The correlation between salivary glucose and blood variables like glycemia and HbA1c were also evaluated in type 2 DM and non-diabetic individuals and had shown inconsistencies in the results. Some studies showed no clear correlation with glycemia or HbA1c,

although other studies in contrary showed good correlation. [23]There have been high to medium strength correlation of salivary glucose with glycemia in some studies [24]and few other studies show a weak correlation. [25]

This shows that duration of the entry of glucose into the salivary glands can also play a role in the increased correlation of salivary glucose levels to the blood glucose levels. Similar study which was performed with five sets of experiments which consisted of different groups of individuals and different methods of analysis of the glucose levels in the blood and saliva. They reported that the salivary glucose concentration increased as blood glucose levels increased and also in normal subjects when there was a comparison between unstimulated and stimulated saliva, it was found that there was a decrease in salivary glucose concentration, increase in salivary flow whereas there was an unchanged glucose excretion rate in stimulated when compared to unstimulated saliva. However in diabetics, there was unchanged salivary glucose concentration and glucose excretion rate in both stimulated and unstimulated saliva. There was also no significant correlation between glycemia and either glucose concentration or glucose excretion rate in diabetics, whether stimulated or unstimulated saliva. [26]Salivary glucose was also estimated using parotid saliva which showed a statistically significant result and correlation on comparison of salivary and blood glucose levels. [27]

With respect to the diagnostic accuracy values of salivary glucose in Type 2 DM in comparison to serum values, a study by Smriti et al. showed the sensitivity and specificity was 99.1% and 93.7% respectively. [28] The literature also reveals another study by Tiongco et al. which showed the values of sensitivity to be 76.0% and specificity 90% respectively. [29]Various other studies have also derived at cut off values of salivary glucose in fasting unstimulated whole saliva samples. According to the same study by Smriti et al., the salivary glucose levels above 7.05 mg/dL may have uncontrolled diabetes mellitus. The study by Tiongco et al. conducted during fasting condition also showed cut off points for salivary glucose as> 13.22mg/dL which may translate the idea that with salivary glucose values more than this may be likely to be diabetic. Unstimulated whole saliva was collected and was observed that if salivary glucose level >11.60mg%, the individual was considered to be diabetic. In another study done by Ephraim et al. that was conducted on newly diagnosed diabetics, 79 diabetic patients were recruited for the study and cut off values for fasting capillary whole blood glucose, fasting serum glucose, fasting salivary glucose were derived. At the cut off value, 76.8mmol/L for FGEG, a sensitivity of 99% and specificity of 100.0% and area under the curve (AUC) of 98.8% was observed for predicting DM while a sensitivity of 80%, specificity of 95% and 85 AUC of 91.0% was observed for fasting salivary glucose at a cut off value of 70.5mmol/L. In addition to that, a cut off value of >6.9mmol/L was derived for fasting capillary whole blood glucose with a sensitivity and specificity values of 100%. [30]

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 need to be conducted towards this perspective.

References

1. *American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009; 32 Suppl 1(Suppl 1):S62-S67.*
2. *Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005; 26(2):19-39.*
3. *DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018; 391(10138):2449-2462.*
4. *Hjerkind KV, Stenehjem JS, Nilsen TILAdiposity, physical activity and risk of diabetes mellitus: prospective data from the population-based HUNT study, Norway. BMJ Open 2017; 7:e013142.*
5. *Khawandanah, J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. Nutr. Diabetes 9, 33 (2019*
6. *Ganesan A, Muthukrishnan A, Veeraraghavan V. Effectiveness of salivary glucose in diagnosing gestational diabetes mellitus. Contemp Clin Dent 2021; 12:294-300.*
7. *Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician. 2015 Apr 1; 91(7):460-7.*
8. *Bansal N. Prediabetes diagnosis and treatment: A review. World J Diabetes. 2015; 6(2):296-303.*
9. *American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care 1 January 2020; 43 (Supplement_1): S14–S31.*
10. *Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. Biomark Insights. 2016; 11:95-104. Published 2016 Jul 3.*
11. *Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol. 2014; 18(1):1-14.*
12. *Patil PB, Patil BR. Saliva: A diagnostic biomarker of periodontal diseases. J Indian Soc Periodontol. 2011; 15(4):310-317.*
13. *Javaid MA, Ahmed AS, Durand R, Tran SD. Saliva as a diagnostic tool for oral and systemic diseases. J Oral Biol Craniofac Res. 2016; 6(1):66-75.*
14. *G.Anuradha, Arvind Muthukrishnan, Vishnu Priya Veeraraghavan. Saliva as a diagnostic fluid in diabetes mellitus- A review. Drug Invention Today.2020.*
15. *Bhattacharyya A, Chandra S, Singh A, Raj V, Gupta B. Salivary glucose levels and oral candidal carriage in Type 2 diabetics. J Oral Biol Craniofac Res. 2018;8(3):158-164.*
16. *Kartheeki B, Nayyar AS, Ravikiran A, Samatha Y, Chalapathi KV, Prasanthi M, et al. Salivary glucose levels in Type 2 diabetes mellitus: A tool for monitoring glycemic control. Int J Clinicopathol Correl. 2017; 1:7-14.*
17. *Harrison R, Bowen WH. Flow rate and organic constituents of whole saliva in insulin dependent diabetic children and adolescents. Pediatr Dent. 1987; 9:287-91.*
18. *Lopez ME, Colloca ME, Paez RG, Schallmach JN, Koss MA, Chervonagura A. Salivary characteristics of diabetes children. Brazilian Dental Journal. 2003; 14 (1):26-31.*

19. *Soares MS, Batista-Filho MMV, Pimentel MJ, Passos IA, Kustner EC. Determination of salivary glucose in healthy adults.Med Oral Patol Oral CirBucal. 2009; 14:e510-13.*
20. *Carda C, Mosquere-Lloreda N, Salom L, Gomez de Ferraris ME, Peydro A. Structural and functional salivary disorders in type 2 diabetic. Med Oral Patol Oral Cir Bucal. 2006; 11 (4): E309-E314.*
21. *Agrawal R.P, Sharma N, Rathore M.S, Gupta V.B, Jain S, Agarwal V, Goyal S. Noninvasive method for glucose level estimation by saliva. J. Diabetes Metab. 2013, 4, 266.*
22. *Amer S, Yousuf M, Siddiqui PQ, Alam J. Salivary glucose concentrations in with diabetes mellitus: a minimally invasive technique for monitoring blood glucose levels. Pak J Pharma Sci. 2001; 14:33-7.*
23. *Darwazeh AM, Farlane TW, McCuish A, Lamey PJ. Mixed salivary glucose levels and candidial carriage in with diabetes mellitus. J Oral Pathol Med. 1991; 20 (6):280-3.*
24. *Jurysta C, Bulur N, Oguzhan B, Satman I, Yilmaz TM, Malaisse WJ, Sener A. Salivary glucose concentration and excretion in normal and diabetic subjects. J Biomed Biotechnol. 2009; 2009:430426.*
25. *Borg A, Birkhed D. Secretion of glucose in human parotid saliva after carbohydrate intake. Scand J Dent Res. 1998; 96:551-6.*
26. *Smriti K, Pai KM, Ravindranath V, Gadicherla S, Pentapati KC. Salivary glucose as a diagnostic marker for diabetes mellitus. J Diabetes SciTechnol. 2016; 10:991-2.*
27. *Tiongco RE, Bituin A, Arceo E, Rivera N, Singian E. Salivary glucose as a noninvasive biomarker of Type2 diabetes mellitus. J Clin Exp Dent. 2018; 10 (9):e902-7.*
28. *Ephraim RKD, Anto EO, Acheampong E, Fondjo LA, Barnie RB, Sakyi SA, Asare A. Fasting salivary glucose levels is not a better measure for identifying diabetes mellitus than serum or capillary blood glucose levels: comparison in a Ghanaian population. Heliyon. 2019 Mar 2;5(3):e01286.*