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ORIGINAL RESEARCH

Saliva as a Potential Diagnostic and Monitoring Tool in Diabetes Mellitus

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Abstract

The salivary fluid has an old history of study but its physiological importance has only been recognized recently. In the past 50 years, pace of salivary research has accelerated with advent of new techniques that have illuminated biochemical and physico-chemical properties of saliva. The recent introduction of molecular biology opens up, once again, new vistas and a new search of the role of salivary fluid as a potential diagnostic tool which has an added advantage of being non-invasive. The role of saliva in the diagnosis as well as monitoring of glycemic control has, also, been attracting attention of clinical researchers in recent times, although, results obtained have largely been conflicting. The present review gives an insight into the possible use of salivary fluid for monitoring of sera glucose levels and thus, in the detection of glycemic control in diabetic patients with evidence of its reliability based on the existing literature.

Keywords: saliva, diagnostics, systemic diseases, diabetes mellitus, un-controlled diabetics, controlled diabetics

1 | INTRODUCTION

The salivary fluid has an old history of study but its physiological importance has only been recognized recently. In the past 50 years, the pace of salivary research has accelerated with the advent of newer techniques that have illuminated the biochemical and physico-chemical properties of saliva. The interest in saliva increased, further, with the finding that saliva is filled with hundreds of components that might serve to detect systemic diseases and/or, act as an evidence of exposure to various harmful substances and provide biomarkers of health and disease. (1–4) Like serum, saliva is a complex biological fluid containing a variety of hormones, antibodies, enzymes, antimicrobial and growth factors. Many of these enter saliva from the serum by passing through the spaces between the cells by trans-cellular (passive intra-cellular diffusion and/or, active transport) and/or, para-cellular (extra-cellular ultra-filtration) routes, thus, making saliva functionally equivalent to serum in reflecting the physiological status of body. (2, 3) The pace of research in relation to the salivary diagnostics and proteomics, however, could not reach the extent that was expected with the advent of newer techniques in the recent decades. The major problems in clinical salivary diagnostics are attributed mainly to the non-standardized collection procedures and difficulty in interpretations due to huge variations in the flow rate and composition of saliva in various systemic diseases and even, under varying physiological conditions. The major advantages, on the contrary, of using saliva as a diagnostic fluid are its non-invasiveness, ease of collection, no requirement of special equipments and/or, trained staff, its usefulness in blood dyscrasias along with a likely better compliance with the children and geriatric patients. (4–6) The role of saliva in the diagnosis as well as monitoring of glycemic control has, also, been attracting attention of clinical researchers in recent times, although, results have largely been conflicting. The present review provides an insight into the possible use of salivary fluid as a potential diagnostic and prognostic tool for monitoring sera glucose levels in detection of glycemic control in diabetic patients with evidence of its reliability based on the existing literature.

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2 | MATERIALS AND METHODS:

The present review was based on a systematic search of all PubMed/Scopus/Web of Science indexed database with key words saliva, diagnostics, systemic diseases, diabetes mellitus, un-controlled diabetics, controlled diabetics. Quick reading of abstracts was conducted and significant articles were kept for review. In addition, cross references which seemed to be clinically relevant were, also, accessed. All original articles, reviews and letters to editor in English literature were included for the present review.

3 | DISCUSSION:

Glucose diffuses easily through the membrane of blood vessels, passes through the blood into the gingival crevicular fluid (GCF) and enters saliva by way of gingival sulcus. There is a controversy, though, regarding the relationship between the concentration of glucose in the blood and that in saliva while a plethora of factors have been cited as being the possible reasons for the poor correlation seen between the blood and salivary glucose concentrations. (7) The prominent among these factors that may account for the poor correlation seen between the blood and salivary glucose concentrations include oral retention of alimentary carbohydrates, glucose utilization by bacteria, release of carbohydrates from salivary glycoproteins and contamination of saliva by a large outflow of gingival crevicular fluid in patients with poor gingival status. (8)

Forbat et al (9) conducted a study to investigate the relationship between sera and salivary glucose levels in diabetic patients using parotid fluid samples and concluded that salivary glucose levels were independent of sera glucose levels. In another similar study conducted by Borg A and Birkhed D (10), the authors, though, observed a significant positive correlation between increased glucose concentration in saliva and sera inspite of using parotid saliva unlike other studies. In yet another study conducted by Darwazeh et al (11) to assess mixed salivary glucose levels and candidal carriage in patients with diabetes mellitus, the authors found glucose concentration in saliva of diabetic patients to be significantly higher than in controls and this was directly related to increased sera glucose levels in diabetic patients. Also, increased salivary glucose levels were found to be associated with increased oral candidal carriage in diabetic patients in the said study.

In similar lines, Belazi et al (12) observed significantly higher concentrations of glucose in saliva with increased sera glucose concentrations in children with IDDM, though, no significant difference in the controls in the unstimulated and stimulated whole saliva samples. In the first of its kind of studies in this regard, Amer et al (13) had, also, suggested complete absence of glucose in salivary samples of non-diabetic subjects while significant concentrations of glucose in salivary samples collected from Type 2 diabetes mellitus patients [non-insulin-dependent diabetes mellitus (NIDDM)]. In similar lines, Lopez ME (14) and Aydin S (15) observed significantly increased salivary glucose levels in patients with diabetes mellitus when compared to controls while in yet another study, Jurysta et al (8) observed increased glucose concentration in salivary samples of diabetic patients though, not in controls in the unstimulated and mechanically, stimulated salivary samples.

Soares et al (7), however, contradicted findings of these studies stating salivary glucose levels were independent of capillary glycemia. Similarly, Vasconcelos et al (16) conducted a study to evaluate the correlation between sera and salivary glucose levels and though, found, salivary glucose concentration to be significantly higher in Type 2 diabetes mellitus patients, could not observe a significant positive correlation between salivary and sera glucose levels in diabetic patients. The authors, therefore, suggested that since salivary glucose levels were not directly influenced by glycemia, salivary assessment of glucose cannot be used to monitor glycemic control in diabetic patients.

Vaziri et al (17), also, observed no significant difference in sera and salivary glucose levels between Type 1 and Type 2 diabetes mellitus patients and controls in their study. Similar to the said models, Hegde et al (18), also, could not find significant variation in salivary glucose levels in diabetic patients and non-diabetic subjects in their study. Likewise, Indira et al (19), also, failed to get a statistically significant correlation between sera and salivary glucose levels in their study, though, they found significantly higher salivary glucose levels in Type 2 diabetes mellitus patients than controls.

Contrary to the findings of these studies, in yet another study conducted by Mirzaii-Dizgah I and Mirzaii-Dizgah M (20) , the authors found a significant positive correlation between sera and salivary glucose levels in diabetic patients and controls concluding that salivary glucose levels may reflect sera values and that salivary glucose levels could be used as an alternative to sera glucose level estimation in diagnosis and regular monitoring of diabetic patients. Balan et al (21) , also, concluded from the findings of their study that salivary glucose levels were significantly higher in diabetic patients than controls and that there was a significant positive correlation between sera and salivary glucose levels in patients with diabetes mellitus. Satish et al (22) , also, observed a significant positive correlation between fasting sera and salivary glucose levels in diabetic patients and controls in their study concluding that saliva could effectively be used in the regular monitoring of glucose levels in diabetic patients.

In yet another study, Shahbaz et al (23) , also, observed elevated salivary glucose levels in Type 1 diabetes mellitus patients compared to controls observing a significant positive correlation between sera and salivary glucose levels in their study. The authors concluded that there are definite changes in salivary composition with increased sera glucose levels in Type 1 diabetes mellitus patients compared with healthy controls and that salivary glucose levels could reliably be used for the regular monitoring of glycemic control in diabetic patients. In accordance with the findings of these studies, a similar study conducted by Vagish Kumar LS (24) observed significantly higher salivary glucose levels in diabetic patients than in controls with a significant positive correlation between sera and salivary glucose levels.

A similar study conducted by Gupta et al (25) , also, observed a significant positive correlation between sera and salivary glucose levels in both diabetic patients and non-diabetic subjects. In similar lines, R Sashi Kumar and R Kannan [26]conducted a study to assess salivary glucose levels and oral candidal carriage in Type 2 diabetes mellitus patients and found higher salivary glucose levels in diabetic patients than in non-diabetic subjects. Furthermore, a significant positive correlation was observed between sera and salivary glucose levels in addition to the finding that increased salivary glucose levels were associated with increased oral candidal carriage in diabetic patients. A very similar study conducted by Kumar et al (27) to check correlation between sera and salivary glucose levels while studying the relationship between salivary glucose levels and oral candidal carriage in Type 2 diabetes mellitus patients, also, found significantly higher salivary glucose levels in diabetic patients when compared against controls while the salivary candidal carriage was significantly higher in uncontrolled diabetics when compared with controlled diabetics and non-diabetic healthy controls.

In another similar study, Panchbhai et al (28) observed significantly increased mean salivary glucose levels in both uncontrolled and controlled diabetic patients when compared with healthy controls. V Nagalaxmi and V Priyanka (29), also, observed a significant correlation between sera and salivary glucose levels in Type 1 diabetes mellitus patients and controls in their study. In similar lines, Naik et al (30) found significantly raised salivary glucose levels in diabetic patients while in yet another study conducted by Panchbhai AS (31) to assess the correlation between sera and salivary glucose levels in diabetic patients, a significant positive correlation between the two was observed.

Similarly, Abikshyeet et al (32) observed increased salivary glucose levels which were found to be in positive correlation with increased sera glucose levels in fasting salivary and sera samples in patients with diabetes mellitus. Based on the results obtained in their study, the authors suggested possible use of fasting salivary glucose levels to precisely predict sera glucose levels in patients with diabetes mellitus. Prathibha et al (33), also, confirmed significant variations in the physical and biochemical parameters of saliva when compared between diabetic patients and non-diabetic subjects in their study. In yet another similar kind of study, Agrawal et al (34) found a statistically significant correlation between fasting sera and salivary glucose levels in diabetic patients and non-diabetic subjects in conformity with the findings of the study conducted by Abikshyeet et al (32). Jha et al (35), also, observed significantly higher salivary glucose levels in diabetic patients than in non-diabetic subjects with a significant positive correlation between sera and salivary glucose levels in the sample studied.

Similarly, Patel et al (36), also, conducted a study to compare sera and salivary glucose levels assessing fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) levels in diabetic patients and non-diabetic subjects and concluded that fasting as well as post-prandial sera and salivary glucose levels were found to be significantly higher in diabetic patients than healthy controls in accordance with the findings of the studies conducted by Abikshyeet et al (32) and Agrawal et al (34). Likewise, Akasapu et al (37) , also, observed a significant positive correlation between sera and salivary glucose levels in their study while the salivary glucose levels showed a proportional increase in the concentration of glucose with an increase in sera glucose levels in diabetic patients. Gupta et al (38) , also, concluded from their study that with an increase in sera glucose levels, an increase in salivary glucose levels was observed in diabetic patients suggesting that salivary glucose levels could be used as a potential diagnostic tool for monitoring glycemic control in diabetic patients.

In a similar study conducted by Shaik et al (39) to check the correlation between sera and salivary glucose levels in diabetic patients and non-diabetic subjects and to correlate oral manifestations in diabetic patients with sera and salivary glucose levels, a significant positive correlation was observed between sera and salivary glucose levels in diabetic patients and non-diabetic subjects. Also, a strong positive correlation was observed between sera and salivary glucose levels and oral manifestations seen in Type 2 diabetes mellitus patients. Ragunathan et al (40), also, found a significant difference in salivary glucose levels between diabetic patients and controls in their study while observing a significant positive correlation between sera and salivary glucose levels in diabetic patients and non-diabetic subjects. In a recent meta-analysis conducted by Naseri et al (41) to evaluate correlation between sera and salivary glucose levels in Type 2 diabetes mellitus patients, a significant positive correlation was observed in diabetic patients and non-diabetic subjects.

Limitations of using saliva as a regular diagnostic and monitoring tool: Saliva does have a few limitations as well in being a universal diagnostic and monitoring tool with xerostomia being one of the major constraints in using saliva for diagnostics. Many classes of drugs, particularly, those that have anticholinergic action including antidepressants, anxiolytics, antipsychotics, antihistaminics and antihypertensive drugs might cause a reduction in salivary flow and alter the composition of saliva. (42, 43) A plethora of systemic diseases, too, impact salivary flow rates and composition, one among them being diabetes mellitus itself. The other significant disorders which lead to such alteration in salivary flow rate and composition include various autoimmune and/or, inflammatory conditions such as Sjögren syndrome, primary biliary cirrhosis, graft versus host disease, immunoglobulin (Ig)-G4-related sclerosing disease and degenerative diseases such as amyloidosis. Other common diseases that lead to such changes in saliva include granulomatous conditions like sarcoidosis, infections including human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) and hepatitis C and malignancies such as lymphomas. Developmental disorders affecting salivary glands like salivary gland agenesis or, aplasias, though, being rare, also, count as substantial causes for alteration in salivary flow rate and composition. atients with salivary gland changes after exposure to radiation in the head and neck area for treatment of malignancies, also, pose such challenges (44, 45) .Apart from the above-mentioned constraints in using saliva as a potent diagnostic tool in various diseases including diabetes mellitus, age-related degenerative changes seen in the geriatric population, also, add to a significant fraction of such aging individuals to suffer from a decreased salivary flow rate (age-related xerostomia) (46–50)

4 | CONCLUSION:

A plethora of studies have tried to establish the diagnostic role saliva can have in the regular monitoring of glycemic control in diabetic patients, there have been conflicting reports from various studies in this regard. Though the recent advances in the field of molecular biology provide a new insight into the potential applications saliva can have, further studies are warranted to validate the role of saliva in the screening, diagnosis as well as routine monitoring of glycemic control in diabetic patients.

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