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# Salivary Biomarkers for Dental Caries – A Review

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**ABSTRACT:** Dental caries (tooth decay) is a highly prevalent multifactorial infectious disease that afflicts a large proportion of the world's population. Dental caries is caused by cariogenic microorganisms in the biofilm (dental plaque), which ferment dietary carbohydrates to produce acid, leading to mineral loss from tooth hard tissues and subsequently the destruction of tooth structures. The interaction of microorganisms, diet and host determines the occurance of dental caries. The constituents and properties of saliva plays an essential role in the occurrence and progression of dental caries. Saliva may protect teeth through several mechanisms, such as clearance of food debris and sugar, aggregation and elimination of microorganisms, buffering actions to neutralize acid, maintaining supersaturation with respect to tooth mineral, participating in acquired enamel pellicle formation (which slows down demineralization during acid attack) and antimicrobial defense. Saliva is composed of 99% water and less than 1% solid (mainly electrolytes and proteins). Although salivary electrolytes and proteins account for only a small proportion of saliva, they play various important roles to maintain the oral health and integrity of teeth.Many measurable characteristics of saliva arepotential biomarkers for dental caries. These salivarybiomarkers may be exploited for the prediction, diagnosis,prognosis and management of dental caries, aswell as for evaluating the outcome of therapeutic regimens. This narrative review aims to provide an overview of the current understanding of salivary biomarkers associated with dental caries.

**Keywords:**Biomarkers, protiens, electrolytes, microorganisms,

## I. INTRODUCTION

Dental caries is defined as an "irreversible microbiological disease of calcified tissues of teeth characterised by demineralised inorganic portion and destruction of organic substance of the tooth which often leads to cavitation[1]. It is a multifactorial infectious disease caused by complex interactions between the acid-producing bacteria, fermentable carbohydrates and host factors.Despite being largely preventable, it remains as the mostprevalent chronic disease globally [2]. The prevalence of dental caries in India was determined in National Health Survey 2004 as 51.9% in 5 year-old children, 53.8% in 12 year-old children and 63.1% in 15 year-old teenagers[3].

Dental caries is a complex multifactorial disease which includes the three main factors of epidemiological triad that is agent, host and environment. All the three conditions need to be present for the beginningand progression of lesions. Adequate time must elapse with the three conditions to permit the transistion from a sound surface to white spot or incipient lesion. Agent factors with respect to dental caries include oral cavity which harbours rich and diverse microbial flora. Environmental factors with respect to dental caries can be divided into two general categories. The community and family environments and the local oral environment around the teeth. The community environment determines whether adequate fluoride is available systemically during tooth development from community water supply or another source. Family environment include family knowledge and attitude towards dental care and measures to reduce the dental caries. Local oral environment includes saliva, microorganisms and food residues around the teeth.Host factors with respect to dental caries include teeth and saliva.Thesusceptibility of teeth to dental caries from one surface to other surface. There are several factors affecting tooth susceptibility for dental caries like morphology of teeth, positions of teeth and composition of teeth. Saliva has numerous roles in tooth maintainance. High buffering capacity of saliva neutralizes microbially produced acids on tooth surfaces and in caries lesions. Low fluoride concentration of saliva facilitates remineralisation of enamel surface. It contains several compounds such as lysozymes, lactoferrin, lactoperoxidase system and immunoglobulins which are potentially bacteriostastic. It is supersaturated with calcium and phosphorous and serves as an abundant source in remineralisation [4]. Whole saliva is derived from several sources: 90% of whole saliva is produced by three pairs of major saliva Glands (parotid, submandibular and sublingual) and 10% is obtained from minor salivary glands in the oral mucosa and from nonglandular sources, such as gingival crevicularfluid[5]. Saliva has multiple functions which includes rinsing, solubilization of food substances, bacterial clearance, soft tissues lubrication, formation of bolus, dilution of detritus, swallowing, speech and facilitation of mastication in addition with the above functions it contribute to mucosal coating, digestion and antibacterial defence[6]. Saliva is composed of 99% water and less than 1% solid (mainly electrolytes and proteins). Although salivary electrolytes and proteins account for only a small proportion of saliva, they play various important roles to maintain the oral health and integrity of teeth. In addition, because of microorganisms, their products and diet-related components found in saliva, this oral fluid serves as a unique medium for monitoring all three aspects (microorganisms, diet and host susceptibility) involved in the caries process. Many measurable characteristics of saliva are potential biomarkers for dental caries.These salivary biomarkers may be exploited for the prediction, diagnosis, prognosis and management of dental caries, as well as for evaluating the outcome of therapeutic regimens[5]. An increasing number of molecular markers in saliva can be used for detection of caries risk, periodontitis, oral cancer, breast cancer, salivary glands diseases and systemic diseases as hepatitis, HIV and HCV.Biological markers (biomarkers) has been defined by Hulka and colleagues as “cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids”.They have been classified by Perera and Weinstein based on the sequence of events from exposureto disease as “ biomarkers of exposure” which are used in risk prediction, and “biomarkers of disease” for screening, diagnosis and monitoring the progression of disease. In practice, biomarkers can aid in understanding the cause, diagnosis, progression, regression, or outcome of treatment of disease[7]. Saliva can be used for detection of caries risk, periodontitis, oral cancer, breast cancer, salivary glands diseases and systemic diseases as hepatitis, HIV and HCV[8], therefore this review aims to provide an overview of the current understanding of salivary biomarkers associated with dental caries

## II. OVERVIEW

**Saliva**

Saliva is derived from several sources: 90% of whole saliva is produced by three pairs of major saliva Glands (parotid, submandibular and sublingual) and 10% is obtained from minor salivary glands in the oral mucosa and from nonglandular sources, such as gingival crevicularfluid[5]. Saliva has multiple functions which includes rinsing, solubilization of food substances, bacterial clearance, lubrication of soft tissues, bolus formation, dilution of detritus, swallowing, speech and facilitation of mastication in addition with the above functions it contribute to mucosal coating, digestion and antibacterial defence[6]. High buffering capacity of saliva neutralizes microbially produced acids on tooth surfaces and in caries lesions. Low fluoride concentration of saliva facilitates remineralisation of enamel surface. It contains several compounds such as lysozymes, lactoferrin, lactoperoxidase system and immunoglobulins which are potentially bacterioststic.
It is supersaturated with calcium and phosphorous and serves as an abundant source in remineralisation[4].

**Salivary biomarkers**

Human saliva is composed of 99% water and 1% other compounds, such as electrolytes, mucus, antibacterial compounds, and various enzymes. Apart from various function of saliva, it contribute to mucosal coating, digestion and antibacterial defence. Saliva has several types of inflammatory biomarkers such as IL-1β, -6 and -8, TNF-α and MMP-8 and -9 which are associated with oral diseases as well as systemic diseases. An increasing number is a specific molecular markers for different [6]. Many measurable characteristics of saliva are potential biomarkers for dental caries which is recognized as the primary cause of oral pain and tooth loss. These salivary biomarkers may be exploited for the prediction, diagnosis, prognosis and management of dental caries, as well as for evaluating the outcome of therapeutic regimens[7]

**Table1:Various salivary biomarkers associated with dental caries**

| **Microorganisms in saliva** | **Streptococcus mutans, lactobacilli, other microganisms such as streptococcus sobrinus,actinomycesspp, candida albicans** |
|---|---|
| **Salivary electrolytes** | Calcium, phosphate, bicarbonate, fluoride, copper, magnesium, sodium, potassium |
| **Salivary proteins and peptides** | Immunoglobulins(IgA,IgG,IgM), innate host defense proteins, and peptides |
| **Functional properties of saliva** | Saliva flow rate, saliva pH, buffering capacity, sugar clearance rate |

**Microorganisms in saliva as biomarkers for dental caries**

**Streptoccus as a biomarker of dental caries**

Streptococcus mutans is the most important bacteria responsible for dental caries. It is a group name for the collection of seven different species. Strep.mutans, strep.sobrinus, strep.cricetus, strep.Ferus, strep.rattus, strep.macacae, strep.downei[9].The most important streptococci isolated from tooth caries samples are S.mutans and S. sobrinus. S. mutans is more cariogenic than S. sobrinus because specific cell-surface proteins, which aid in its primary attachment to the tooth are absent in S. sobrinus[10]

**Lactobacillus as a biomarker of dental caries**

Among the Lactobacillus rods in the oral cavity Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus delbrueckii, Lactobacillus plantarum, Lactobacillus jensenii, Lactobacillus brevis, Lactobacillus salivarius and Lactobacillusgasseri are most common. Lactobacilli are isolated from deep caries lesions but rarely before the development of dental caries. It is believed that they are pioneering microorganisms in the caries progress, especially in dentin. Lactobacilli cell surfaces have an Surface layer of proteins. This protein layer has a crystalline structure and is responsible for the surface hydrophobicity. The bacteria are able to adapt their surface hydrophobicity to environmental changes (pH, ionic strength and are able to produce lactic acid can decrease environmental pH until values less than 4.5. These species can survive even in pH of2.2[11]. Studies have shown that Lactobacilli are a dominant part of the flora inhabiting the deep cavities, and their number correlates with the amount of carbohydrates[10]

**Candida albicans as a biomarker of dental caries**

Candida albicans remains the most important fungal pathogen associated with oral candidiasis. C. The mechanisms underlying this pathogenic process are still unclear. It is thought that Candida albicans may degrade the dentinal collagen, probably leading to dentinal lesions. Also, Candida is able to colonize hard tooth surfaces, invade dentinal tubules and produce a large amount of acids and metabolise dietary sugars, provoking demineralization of the dental enamel and dissolution of hydroxyl appetite crystals [12]

**Salivary electrolytes as a biomarkers of dental caries**

Among salivary electrolytes, fluoride, calcium, phosphate and bicarbonate are considered of particular importance for protecting teeth from caries

**Fluorides as a biomarker of dental caries**

Fluoride has 3 main mechanisms of action in reducing the dental caries, it promotes enamel remineralization, it reduces enamel demineralization, it inhibits bacterial metabolism and acid production. The mechanisms of fluoride are both topical and systemic, but the topical effect is the most important, especially over the life span[13]. A clear, inverse relationship between salivary fluoride level and children's caries rate was substantiated[14]

**Calcium and phosphorous as a biomarker of dental caries**

An inverse relationship was found between dental caries and levels of salivary calcium and between dental caries and organic or inorganic phosphorous. This was shown as a lower calcium level in saliva of caries-active teenagers compared with the caries-free group[15,16].

**Zinc as a biomarker for dental caries**

No correlation was found between caries and zinc. Although zinc may reduce enamel demineralization and modify remineralization in experimental studies, further evidence collected from human studies is needed to ascertain the effect of zinc on reducing caries risk[5].

**Iron as a biomarker for dental caries**

Fe have an anticaries effect due to its ability to inhibit the F-ATPase of *S. mutans* which may affect the acidogenicity and aciduricity of *S. mutans*. Fe may reduce the production of extracellular polysaccharides (EPS) by interfering with sucrose metabolism. Moreover, it has been shown that iron inhibits glycotransferase (GTF) enzymes produced by *S. mutans* via an oxidative mechanism involving a Fenton-type reaction[17].

**Trace elements**

Cu had a consistent inverse relationship with caries experience and the concentration of Zn and Mn in saliva did not have any relationship with caries experience. K and Cl were both slightly higher in the caries-active group [14].

**Salivary proteins and peptides as biomarkers of caries**

Saliva contains various proteins and peptides such as IgA, IgG and IgM,Innate (nonimmune) host defense proteins and peptides(acidic proline-rich proteins, mucous glycoproteins, agglutinins,amylase, lactoferrin, lysozyme, peptides, free amino acids) which are biomarkers of dental caries[5]

**Immunoglobulins (IgA, IgG and IgM),**

The immunoglobulins in saliva primarily belong to the IgA subclass (>85%) and to a lesser extent, IgG and IgM subclasses. Altogether,immunoglobulins make up 5–15% of total salivary proteins. They play an antibacterial role by interfering with the adherence of microbial flora to tooth surfaces, inhibiting bacterial metabolism, neutralizing bacterial toxins and enzymes and agglutination of bacteria[5]

**Innate (nonimmune) host defense proteins and peptides**

Saliva contains a plethora of proteins and peptides in widely varying concentrations. Their mechanism of action include inhibiting the adherence, metabolism or viability of cariogenic microorganisms and promoting aggregation, thus eliminating bacteria.The constant and immediate availability has made innate host defense proteins and proteins as a attractive biomarker for therapeuticalpurposes[5].

**Acidic proline-rich proteins**

Proline-rich proteins are a class of intrinsically unstructured proteins that contain several repeats of a short proline-rich sequence. Proline-rich proteins can be divided into acidic and basic families.Acidicproline-rich proteins account for 25–30% of all proteins in saliva, play a role in the formation of dental pellicle and influence initial microbial colonization on tooth surfaces[18]

**Mucous glycoproteins**

Mucins interact with several strains of streptococci and promote their agglutination, thereby accelerating the clearance of bacteria from the oral cavity. As major components of the acquired pellicle, mucins may also interact with dental hard tissues, influence the adhesion of specific bacteria to the tooth surface and therefore affect the microbial composition[19].

**Agglutinins**

Agglutinin is a mucin-like glycoprotein that is known to mediate the aggregation of many oral bacteria in vitro. Agglutinins interact with unattached bacteria, resulting in clumping of bacteria into large aggregates, which are more easily swallowed or flushed away which increase over all clearance of oral bacteria[20].

**Amylase**

Alpha-amylase is the most abundant salivary enzyme and accounts for 40–50% of the total salivary gland produced protein. It has several distinct biological functions that may allow or inhibit the occurrence of dental caries.Amylase is found in acquired enamel pellicle and may modulate the adhesion of bacteria. Amylase effectively attacks random locations along chains of starch and there by break down of long chain carbohydrates into maltose , dextrin. Oral bacteria can ferment maltose to glucose and cause a drop in pH in dental biofilms and from this aspect amylase activity promotes caries development

**Lactoferrin and lysozyme**

Lactoferrin has bacteriostatic, bacteriocidal, fungicidal, antiviral and anti-inflammatory activity. As a strong cationic protein it can activate bacterial autolysins which can destroy the cell walls. Lysozyme can activate bacterial autolysins and destroy the cell walls. Lysosomes are membrane-enclosed organelles that contain an array of enzymes capable of breaking down all types of biological polymers proteins, nucleic acids, carbohydrates and lipids[21]

**Free amino acids**

Free amino acids in human saliva can pass readily into and out of dental plaque fluid. They can be potential metabolic substrates for microflora or products of microorganism metabolism pathways. Some of these molecules play a significant role in the caries process. Free glycine reduced the risk of dental caries, whereas proline increased the risk. The levels of free arginine and free lysine were significantly higher in caries-free adults[5]

**Functional properties of saliva as biomarkers of caries**

**Salivary flow rate**

Salivary flow rate is considered as one of the most important parameters because the cariostatic activity or other salivary functions, such as buffering and clearance, depend on the salivary flow rate. Decreased salivary flow and alterations in salivary composition cause a clinically oral imbalance manifested by increased caries incidence, susceptibility to oral candidiasis, xerostomia, difficulties with speech, mastication and swallowing, altered taste perception and halitosis[22].

**Saliva pH and buffering capacity**

Saliva buffering capacity works by counteracting the decrease in pH and is another factor protective against caries. Bicarbonate is the main component responsible for the buffering capacity of saliva working in conjunction with the phosphate and the protein buffer systems.Buffer capacity is a moderate risk factor for caries prevalence and incidence. It has been documented that the dissolution of enamel occurs when the pH falls below critical pH, i.e. 5.5..pH, buffering capacity are slightly decreased in caries active children compared to caries free children but they had a weak correlation with caries activity[15]

**Salivary sugar clearance rate as a biomarker for dental caries**

Oral sugar clearance (OSC) is the reduction in the concentration of sugar in saliva over time. OSC is dependent on the amount of sugar and the efficiency of its removal, depending on the properties saliva that is saliva flow rate increase in saliva flow rate leads to swallowing and elimination of sugars from oral cavity. For each swallow the sugar rate decreases gradually. Several studies have revealed associations between OSC and oral function, salivary secretion, buffer capacity, and cariogenic micro-organisms, However none of studies has analyzed whether the inclusion of OSC improves the ability to predict the prevalence of dental caries[23]

## III. CONCLUSION

Saliva biomarkers have many potential roles in the diagnosis and management of dental caries. A few salivary tests, such as salivary flow rate, buffering capacity and bacterial tests (for S. mutans and lactobacilli) have entered dental clinical practice and can be used to assist the assessment of patients' caries risk. Yet no salivary biomarker identified so far is able to select caries- susceptibility in patients with high sensitivity and specificity on a single test basis. Various salivary parameters should be combined with socio-demographic, behavioral and clinical factors for a better estimate of patients caries risk assessment.

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