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Salivary Biomarkers of Dental Caries –A Review Article

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Abstract: *Dental caries is a highly prevalent multifactorialinfectious disease that afflicts a large proportionof the world's population. Detecting pathologies at their earlieststages can significantly affect patient discomfort, prognosis, therapeuticintervention, survival rates, and recurrence. Saliva has the potential to be used in the early detection and diagnosis of caries. This is due to the abundant biomarkers presentin saliva. This paper is aimed to compose a systematic review about the potential salivary biomarkers of dental caries*

Keywords: *Caries Susceptibility, Microorganisms, Presymtomatic State, Proteins, Salivary Biomarkers.*

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I. Introduction:

Dental caries is recognized as a multi-factorial infectious disease caused by complex interactions among acid-producing bacteria, fermentable carbohydrates and many host factors including saliva. The costs of treating dental caries and its complications impose heavy financial burdens on individuals, families and society as a whole. 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 oral cavity is an intricate environment composed of multiple structures and tissues types working in concert. While each structure performs a unique function, all are colonized by bacteria and immersed in salivary fluids. The interplay between microorganisms, diet and host susceptibility determines whether dental caries will occur.

PROPERTIES OF SALIVA:

Human saliva is a clear, slightly acidic (pH 6.0 to 7.0) heterogeneous biofluidcomposed of 98% water and 2% othercompounds, such as electrolytes, mucus, antibacterial compounds,and various enzymes[1,2].Saliva is also a complex mixture of oral fluids which is composed of salivary gland secretions, gingival crevicular fluid, expectorated bronchial and nasal secretions, serum and blood derivatives from oral wounds, bacteria and bacterial products, viruses, fungi, desquamated epithelial cells, other cellular components, as well as food debris[3,4]. On average, individual salivation can range from 0.3 to 0.7 ml of saliva per minute,producing a range of 1 to 1.5 litres daily.90% of whole saliva is produced by three pairs of major salivary glands (parotid, submandibular and sublingual) and 10% is obtained from minor salivary glands in the oral mucosa and from nonglandular sources, such as gingival crevicular fluid.

Each salivary gland is highly permeable and enveloped by capillaries, a feature that allows for the free exchange of bloodbased molecules into the adjacent saliva-producing acinuscells[5]. Researchers postulate that blood-derived molecules entering salivary tissues via transcellular (e.g., passive and active transport) or paracellular (e.g., extracellular ultrafiltration) routes could potentially influence the molecular constituency of oral fluids[6]. This suggests that circulating biomarkers of disease absorbed by the salivary glands may possibly alter the biochemical composition of salivary secretions. Consequently, oral fluids may contain molecular information capable of communicating an individual's current state of health.

Saliva as a mirror of oral and systemic health is a valuable source for clinically relevant information. Saliva is easy to collect, to store, and can be obtained at low cost in sufficient quantities for analysis. One of the most important property is that collection of saliva is a non-invasive method. Saliva may also be potentially

used for the diagnosis of HIV, breast cancer, diabetes, arthritis and heart disease, and it is expected to become a mean of diagnosis at the same level of blood or urine analysis[7].

Various protective functions of saliva
-Cleaning teeth,
-Protecting against abrasion and attrition,
-Retarding demineralization as well as promoting remineralization,
-Rapidly neutralizing acids,
-Defending the oral cavity from infection.
- Saliva also affects taste sensation
Each protective function may involve several salivary constituents, and some salivary components contribute to more than one protective function.

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II. Functional Properties Of Saliva As Biomarkers Of Caries

1. Salivary flow rate

The salivary flow is important in the prevention of caries, and there is a high risk of caries in individuals with a low unstimulated salivary flow[8]. Practically all other salivary functions, such as buffering and clearance, depend on the salivary flow rate. Cavities are most prevalent in patients with a lower salivary flow due to a decrease in the antibacterial, buffering and cleansing functions. The salivary flow dilutes the substances, cleans the oral cavity off carbohydrates, non-adherent bacteria, desquamated epithelial cells and food debris. This phenomenon is essential for decreasing the availability of sugars for the biofilm.The salivary viscosity reduces the hydration capacity of saliva, and consequently raises the caries risk.

Criteria used for hyposalivation include ‘whole stimulated saliva below 0.7 ml/min or whole unstimulated saliva below 0.12–0.16 ml/min’[9], ‘unstimulated flow rates lower than 0.1 ml/min’ [10] or ‘0.30 ml/min’ [11] and ‘45% reduction in a person’s stimulated salivary flow rate[12].

Treatments as radiotherapy affect the salivary glands, and these conditions result in alteration of quantity, quality and composition of saliva. In autoimmune disease likeSjogren’s syndrome salivation is reduced. Various medicines have an anticholinergic action, which reduces the salivary flow. Carious lesions developed rapidly among these individuals and also on tooth surfaces usually not susceptible to caries. Lack of saliva predisposes the development of atypical or unusual dental decay i.e., cervical, incisal or in cusps tips, as well as radicular lesions[13].

Clinical trials on saliva stimulation by chewing sugar-free gum after meals showed a significant decrease in caries incidence and that the benefit was attributable to stimulating salivary flow rather than to any chewing gum ingredient.

2. Saliva pH and buffering capacity

The quantitative assessment of resistance to pH changes is referred to as buffer capacity. There is strong evidence to indicate that salivary buffering capacity protects the tooth from dental caries. Saliva buffering capacity works by counteracting the decrease in pH and is another factor protective against caries**.**

Saliva has two main buffer systems; 1st isthe carbonic acid-bicarbonate system is the most efficient in stimulated saliva and 2nd is phosphate buffer system which is efficient in unstimulated saliva.[14,15].
Bicarbonate in saliva serves as the main buffer against acid, working in conjunction with the phosphate and the protein buffer systems.

Low buffering capacity is usually associated with caries development because of its impaired neutralization of plaque acids and reduced remineralization of early enamel lesions. Individuals with a high salivary buffer capacity are often caries-resistant.

III. Microorganisms

Cariogenic bacteria are usually present in relatively small quantities in healthy saliva and plaque. However, with biological and environmental changes such as the increased frequency of fermentable carbohydrate consumption, conditions of low pH will favour the proliferation of bacteria [16]. As caries is an infectious disease, the colonization, proliferation and metabolism of cariogenic (aciduricand acidogenic) bacteria have been extensively exploited for identifying caries-prone individuals. The 'specific plaque hypothesis' proposes a few specific species of bacteria as being responsible for caries, the 'ecological plaque hypothesis' considers caries as an outcome of the overall activity of a heterogeneous mixture of microorganisms and a cariogenic shift of the plaque microbiomes [17].The acidic metabolites by microorganisms cause a local pH fall below a critical value (pH 5.5) resulting in the demineralization of the tooth tissue. The demineralization process consists of dissolution of the hydroxyapatite crystals, the major component of tooth enamel and dentin, by organic acids that diffuse into the tooth

Mutans streptococci and lactobacilli

The main responsible bacteria for this disease are the endogenous strains *Streptococcus mutans, Streptococcus sobrinus*and *Lactobacillus species,* present in the biofilm. A central role of mutans streptococci in the initiation of caries has been well established due to formation of extracellular polysaccharides from sucrose which fosters their firm attachment to teeth andpromotes tight cell clustering, rapid fermentation of carbohydrates to acids and tolerance tolow pH.Mutansstreptococci include bacteria of seven species, namely Streptococcus mutans, Streptococcus sobrinus, Streptococcus cricetus, Streptococcus rattus, Streptococcus ferus, Streptococcus macacae and Streptococcus downei [17]. Among these species, S. mutans has been identified as a strong pathogen for caries; however, other species, such as S. sobrinus, may also playa role. Early acquisition of S. mutans is associated with early childhood caries and future caries

As a late colonizer, lactobacilli may not be a requisite for caries initiation. However, they may potently contribute to caries progression once lesions are established [18]. As the level of lactobacilli in saliva also appears to reflect the acidogenic conditions associated with the consumption of abundant simple carbohydrates, it could serve as a useful indicator fora cariogenic diet. For mutans streptococci that are indicative for elevated caries risk, both 10^5 [19] and 10^6 [20] colony forming units per milliliter of saliva were suggested; whereas for lactobacilli, counts of 10^3, 10^4, 10^5 [20] and 10^6 colony-forming units per milliliter of saliva have been proposed.

Conventional bacterial test kits are almost exclusivelyculture-based, using dip-slide or selective culturebroth. They are not highly specific for the targetbacterial species and require a few days of incubationbefore a result is available. Some novel test kits, usingimmunoassay technology, have recently been developedand are expected to provide quick and highlyspecific numeration of cariogenic bacteria.

Other microorganisms

The range of bacteria potentially involved in caries also include some nonmutans streptococci, such as Streptococcus sanguinis and Streptococcus salivarius, and Actinomycesspecies ; the latter contributes to the onset of root surface caries [21, 22].

Although bacteria are considered the main pathogens for dental caries, some studies have suggested that Candida albicans makes a significant contribution to caries pathogenesis, particularly in children, adolescents and young adults. Thiswas attributed to its acidogenicity, capabilities of forming hyphae and the secretion of dentine-degrading enzymes

It is believed that over 50% of bacteria in the oral cavity cannot yet be cultivated, hampering our understanding of microbial activities in respect to dental caries. However, emerging technologies, such as checkerboard DNA–DNA hybridization, genomic fingerprintingand 16S ribosomal RNA gene cloning and sequencing, together with the rapid expansion of bacterial genome data, have made it possible to evaluate the diversity of the human salivary microbiome and its association with dental caries.

IV. Salivary Electrolytes

Among salivary electrolytes, fluoride, calcium, phosphateand bicarbonate are considered of particularimportance for protecting teeth from caries.The presence of fluoride in saliva is very important because it reduces acid production in the biofilm [14].Fluoride, calcium and phosphate ions keep salivasupersaturated with respect to hydroxyapatite andoffer a reparative and protective environment formaintaining the integrity of dental tissues [23]. Saliva modulates the phenomena of remineralization and demineralization. These phenomena are controlled by the concentration of salivary calcium, phosphate, fluoride, and pH.An inverse relationship was found between dentalcaries and levels of salivary calcium, andbetween dental caries and organic or inorganic phosphorous.A study measuringsalivary electrolytes in 272 children with a varyingcaries rate showed an inverse relationship betweendental caries and copper, an inconsistentassociation between caries and magnesium or iron,and no correlation between caries and zinc [24].

V. Salivary Proteins (Proteome)

The salivary proteome is composed mainly by proteins involved in oral biochemistry, and more than 1400 proteins were already identified. The characterization of salivary proteome associated with dental caries can be an important step towards the identification of biomarkers to caries and to predict caries susceptibility, allowing the intervention in a presymptomatic state. Saliva is composed by various proteins essential for the oral health, because many proteins present antimicrobial activity. Changes in salivary proteome can provide changes in microbial flora, and consequently lead to caries progression.

1. Immunoglobulins

The immunoglobulins in saliva primarily belong to the IgA subclass (>85%) and, to a lesser extent, to the IgG and IgM subclasses. Altogether, immunoglobulins make up 5–15% of total salivary proteins. Salivary antibodies are the first line of immune defense against antigens present in saliva [25].They play an antibacterial role by inhibiting bacterial metabolism, neutralizing bacterial toxins and enzymes and agglutination of bacteria. In addition, it promotes the inhibition of bacterial adherence, by the reduction of the hydrophobicity of bacteria. Also, it act synergistically with other defense mechanisms, such as the lactoferrins, peroxidases, agglutinins and mucins.The normal level of sIgA (Salivary IgA) in individuals without systemic or immunological diseases ranges from 4-30 mg/dL [26]. This level is changed by numerous conditions, like malnutrition, obesity, infections, stress, smoking, salivary flow rate, hormonal factors, emotional states and physical activity. In elderly people, a decreased level of sIgA is associated with an increase in root caries and candidiasis.

Some studies report an inverse relationshipbetween total salivary IgA concentration [26] and caries experience a positive correlation [27]and no clear relationship [28] werefound in other studies. Similarly, although specificIgAs (e.g. anti-S. mutans IgA) have been linked todental caries, an inverse relationship, a positive correlation or no relationshiphave been reported. Salivary IgA antibody responses to mutans streptococci can be observed in early childhood.

Controversy also remains in research on IgG andIgM as biomarkers for caries. Recentstudies showed no correlation between IgG and caries [29]. A protective role of anti-streptococcal IgGsagainst colonization of S. mutans and caries has beensuggested by some experimental evidence [30]. However, in another study, the level of anti-S.MutansIgG appeared to be directly proportional to the cariesincidence.

Studies on the relationship between immunoglobulinsand caries have several methodological limitationsthat make it difficult to draw conclusions. Mostof the studies are cross-sectional with a small numberof subjects. This may limit the statistical power and the possibility of establishing any causal relationship.Synthesizing results from different studies is difficultbecause of the large heterogeneity of the studydesign, the source of saliva (whole saliva or specificglandular secretions), methods used to stimulate salivasecretion (chewing unflavored wax or rubberbands, use of 2% citric acid or lemon candy, or nostimulation),

2. Acidic proline-rich proteins

Proline-rich proteins are a class of intrinsicallyunstructured proteins that contain several repeats ofa short proline-rich sequence. Proline-rich proteinscan be divided into acidic and basic families. Theacidic proline-rich proteins possess a 30-amino-acidN-terminal domain that is rich in aspartate and glutamatewith a few serine phosphate residues [31]. This domain adheres strongly to recently cleaned toothsurfaces. Acidic proline-rich proteins account for25–30% of all proteins in saliva and play a role in the formationof dental pellicle and influence initial microbialcolonization on tooth surfaces. Buffering capacity, antibacterial property and lubrication is exerted byproline-rich glycoproteins. Proline-rich proteins, bind to hydroxyapatite of enamel crystals and inhibit the precipitation of calcium and phosphate. Proline-rich proteins play an important role in the inhibition of the spontaneous precipitation of calcium and phosphate ions in salivary glands and saliva, and in the formation of dental calculus.

3. Mucins 1 e 2 (Mucous glycoproteins)

Mucous glycoproteins (mucins) constitute a family with two members, namely high-molecular-weight mucins (MG1) and low-molecular-weight mucins (MG2).There is inverse relationship between Mucins 1 and 2 levels and the prevalence of dental caries.The mucins of saliva form a seromucosal cover that protects, lubricates, prevent the dehydration and maintain the viscoelasticity of saliva [14]. It also protects tissues against the proteolytic attacks of microorganisms. It has antibacterial properties.Mucins interact with several strains of streptococci and promote their agglutination, thereby accelerating the clearance of bacteria from the oral cavity [32].The mucins are present in acquired pellicle from tooth surfaces and protect teeth surface from demineralization.

4. *Agglutinins*

Salivary agglutinin is a mucin-like glycoprotein that is known to mediate the aggregation of many oral bacteria. Agglutinins interact with unattached bacteria, resulting in clumping of bacteria into large aggregates, which are more easily swallowed or flushed away [33].

Low concentration (0.1%) of agglutinin in saliva that makes it difficult to extract from saliva and thus very few studies are done on agglutinins.

5. Lactoferrin and lysozyme

Lactoferrin competes with various microorganisms in binding to free iron; this competition mechanism has a bacteriostatic and bactericidal effect on various microorganisms that depend on this ion to survive [14].Lactoferrin has bacteriostatic, bacteriocidal, fungicidal, antiviral and anti-inflammatory activity.

Lysozyme can activate bacterial autolysins and destroy the cell walls. Lysozyme is an enzyme that destroys the bacterial cell wall of some bacteria.

6. Cystatin S and Statherin

Saliva presents seven different cystatins, cystatinA, cystatin B, cystatin C, cystatin D, cystatin S, cystatin SA and cystatin SN [34].These proteins are cysteine protease inhibitors, and are mainly present in submandibular saliva.The capacity of oral protection of Cystatins is thought to be related to the inhibition of cysteine proteases.Cystatin S can be phosphorylated in five sites. The phosphorylated forms have an important function in the regulation of calcium levels and in the pellicle formation. The removal of the phosphate groups of cystatin reduces the affinity of the protein to hydroxyapatite. Statherin has many functions, the most important being the inhibition of precipitation in supersaturated solutions of calcium [35]. Therefore, it is the primary regulator of mineralization in the oral cavity. This characteristic is due to the negatively charged phosphorylated N-terminal.

These proteins have an inverse correlation with occlusal caries. Higher levels of statherin and cystatin S are observed in caries-free individuals.

7. Defensin

Defensins are small, cationic proteins with antimicrobial activity. The bacterial charge is an important factor for the susceptibility of bacteria to cationic peptides. These peptides are able to kill a variety of gram-positive and gram-negative bacteria, fungi and enveloped viruses [36].Defensins can be divided in two subfamilies, including α-defensins and β-defensins.

Higher salivary a-defensins (HNP1, 2, 3) have been detected in caries-free children than in children affected by caries.

8. CD14

It is involved in innate immunity that act as a receptor of lipopolysaccharide (LPS) or peptidoglycan (PGN) of gram-negative and gram-positive bacteria, respectively. The LPS/PGN-CD14 complex binds to Toll-Like receptors of polymorphonuclear cells and activates the production of inflammatory cytokines by multiple signaling pathways [37]. It mediates the activation of endothelial cells, epithelial cells and polymorphonuclear leucocytes.

Major salivary glands secrete sCD14 into saliva. CD14 acts as an important anti-cariogenic factor. An inverse relationship is observed between the presence of sCD14 in saliva and caries lesions. It enables the binding between the epithelial cells and bacteria and activates the production of cytokines for the recruitment of phagocytes.

9. Glucosyltransferases

The dental caries is an infectious disease and studies indicate that can be preventable with mucosal immunization.Glucosyltransferases (GTFs) from S. mutans are a candidate for the production of dental caries

vaccine [38].These proteins are important for the synthesis of glucans. These glucans serve as a binding site for streptococci and others microorganisms. Glucans participate in oral colonization and formation of the oral biofilm.

The S. mutans have three types of GTFs with different functions and localization. GTF B and GTF C are associated to cell wall, while the GTF D is secreted.GTF B produces soluble glucans, which play an important role in the development of dental caries.GTF is directly related to caries production.

10. Amylase

Growth inhibiting factor is a high-molecular-weight glycoprotein-α-amylase complex able to inhibit GTF from S.mutans. Consequently, it helps in the control of S.mutans colonization. Digestion is initiated in the oral cavity by the enzyme α-amylase. The α-amylase is referred to as a good indicator of the function of the salivary glands, and represents 40% to 50% of the protein content of saliva [14]. 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 bound to bacteria in plaque may facilitate hydrolysis of dietary starch to provide glucose for metabolism by plaque microorganisms in close proximity to the tooth surface. In addition, amylase may bind with high affinity to a selected group of oral streptococci and contribute to bacterial clearance.

However Balekjian et al. observed that a caries-rampant group exhibited a significant reduction in the salivary level of basic proteins and a significant increase in amylase compared to a caries-free group [39].

VI. Conclusion

The dental caries affect the salivary proteome. Consequently saliva appears to be a potential source of biomarkers for dental caries.

Further studies are needed to define whether the individual has an increased risk of caries.

No salivary parameter identified thus far is able to select caries-susceptible patients with high sensitivity and specificity on a single test basis. Various salivary parameters should be combined with sociodemographic, behavioral and clinicalfactors for a better estimate of patients' caries risk.

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