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Review Article

Salivary Proteins Roles in Dental Caries Review Article

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Abstract

Introduction: This work describes the current state of research on the role of salivary proteins in dental caries which causes irreversible damage in dental tissues. To date, no evidence is comprehensively proving that salivary proteins could serve as potential indicators for early diagnosis of the risk factors which lead to dental caries.

Aim of the Work: This review article aims to clarify the correlation between salivary proteins and dental caries.

Methodology: This review is comprehensive research of PuBMED and Google Scholar from the year 1979 to 2023.

Conclusion: The maintenance of oral health and protection from tooth erosion is one of the most important functions of human saliva. Salivary proteins play an essential role in maintaining oral health and dentition intact. Several studies have investigated the correlation between these proteins and dental caries occurrence. The relationship between a protein or group of proteins and the occurrence of dental caries were mentioned in a few studies and most of these results are controversial. As a multifunctional disease, associating caries with only one risk factors is probably not promising and a more complex association should be sought.

Keywords: *Salivary Protein; Dental Caries; Oral Health*

Introduction

Dental caries and periodontal diseases are considered the most frequent chronic diseases in the oral cavity [1,2].

Although there is massive reduction in the recorded rates of dental caries still it is a serious oral health issue that occur in about 60 - 90% of children and adults.

Reflecting a significant effect on general health and quality of life [3,4].

All age groups represent several manifestations of dental caries [5-7].

Dental caries occurs due to interaction between oral microorganisms and fermentable carbohydrates leading to increase the acidity inside the oral cavity [8,9].

As a multifactorial disease, the properties of saliva [10], genetic predispositions [11,12], age and immunological status [13], and behavioral factor like nutrition and hygiene habits [14].

A comprehensive understanding is required in dental researches of the prevention, treatment and management of oral diseases.

Over the years, however, oral diseases including dental caries were considered a local illness.

Recently, they can be determined by general health status [15].

Research has also shown that oral health, in turn, plays a role as pathogenetic determination of medical disorders [16,17].

Modern discoveries support the relationship between oral diseases and general health. A complete understanding of the pathophysiology of oral disease, is important for predicting, evaluating risk and suggesting possible treatments, to be achieved.

Assessing the risk of caries, however, would allow for estimation of the probability of its incidence, i.e. the number of new cavities or lesions within a certain period, and the probability of changes in their size or activity [19].

To increase the prevention and treatment efficiency, an exact assessment of the possible formation of tooth decay must be established and may help to identify high-risk patients.

By using state-of-the-art methodologies, intense investigations of protein functions in saliva as indicators for predicting disease risk has begun.

Thus, we aim to provide an overview of the benefits of salivary proteins along with up-to-date proteomic approaches used for the identification and assessment of protein risk factors connected to dental caries.

Saliva

Human saliva is used to monitor general health, disease onset and progression of the disease. Protein biomarkers may provide valuable information accurately and reproducibly on the body response to a treatment for a disease or condition, including the long-term monitoring of oral disease.

They can further act as an early indicator of disease, which is good alternative to other oral diagnostic approaches [20].

Composition

Saliva is a mixture of secretions from all the glands present. Human saliva contains less than 1% total solids.

The ions present include Na^{+}, K^{+}, Mg^{2+}, Po_4^{-3} and HcO_3^{-}.

It is absolutely supersaturated with calcium and phosphate salts which help in the prevention of demineralization of the teeth. Proline-rich proteins and Statherin inhibit the precipitation of calcium phosphate crystals from supersaturated saliva onto the teeth, are also present.

The salivary flow rate affects the alkalinity or acidity of saliva but the PH is usually within range 6.2 to 8.0. About 50 different proteins, in saliva are around, the major ones being the enzyme amylase and mucins present in smaller amount include the enzyme lysozyme and sialoperoxidase, lactoferrin, histatins and various immunoglobulins, all of which have protective functions in the mouth [21].

Generally, saliva is secreted at a rate 0.3 ml to 7 ml/min. In a healthy person, the flow of whole saliva can reach an average of 1 - 1.5L per day [22,23].

Salivary components and the volume depend on circadian rhythm [24-27], the activity and stimulation of various saliva-producing glands [28,29], age, gender, blood type of the patient [30,31] and physiological stimuli [32,33].

The importance of saliva is often over-locked; however, it has severe critical roles in the caries process. The major and the minor glands excrete saliva at different rate and different constituents depending on the presence or absence of stimulatory factors.

Calcium and phosphate ion concentrations increase in saliva stimulated by chewing. A gustatory effect such as that induced by some food acid, has been shown to stimulate a higher flow rate of saliva than stimulated mechanical chewing.

Saliva helps to balance the caries process and has critical role in remineralization. It provides a supersaturated solution of calcium ions and fluoride ions from extrinsic sources [34].

The major constituent of saliva is water (99.5%), with a wide range of other inorganic and organic components, the most relevant being the salivary proteins which provide:

- Antibacterial and antiviral activity.
- Lubricant, which also assists in bolus formation.
- Inhibition of demineralization and stabilization of calcium and phosphate ions which assists remineralization.

Therefore, a decrease in the amount of saliva can significantly increase the caries risk [34].

Time

On the occurrence of acid challenges repeatedly, the eventual collapse of enamel crystals and subsequently rods will result in surface breakdown and dental caries formation. This process may take months to years, depending on the intensity and frequency of acid attack. This means that, in all mouths there is continual demineralization of enamel; therefore, an individual is never free of dental caries [34].

The process of enamel demineralization and remineralization are constantly cycling between net loss and gain minerals. When the balance directed towards net loss that clinically signs of process become apparent. The long-term outcome of this cycling is determined by:

- Dental plaque composition and amount.
- Frequency and timing of sugar consumption.
- Fluoride exposure.
- Salivary flow and quality.
- Enamel quality.
- Immune response.

Thus, the term caries-free is best changed to the term caries-inactive to be more accurately reflect clinical reality [34]. For the balance to be maintained, there should be sufficient time between cariogenic challenges for the mineralization process to take place. When these challenges become too frequent, or occur when salivary flow is reduces, the rates of demineralization and subsequent tooth breakdown will increase [34].

Functional properties of saliva

Saliva is a complex fluid where various constituents alone or in concert to perform different functions in oral cavity. Functions of saliva are divided into buffering action, lubrication, maintenance of teeth integrity, antibacterial activity, taste and digestion.

The net buffering capacity of stimulated whole saliva relies on several buffering systems. The buffering activity of the carbonic acid/bicarbonate system is the most important for neutralizing acids.

Phosphate ions contribute, mainly during unstimulated, low-flow rates. Some proteins and urea add to saliva's buffering capacity [35].

Saliva viscosity is providing lubrication for the tongue movement during eating, swallowing and speech. Mucins are the most important for lubricating oral surfaces. They have high viscosity and elasticity, strong adhesiveness, and lubricate hard and soft tissue surfaces.

Saliva is composed of variety of electrolytes, exosomes, micro RNA, and cytokines which are crucial biomarkers in oral and systemic diseases detection. Saliva also has anti-microbial activity, regulating bacterial and fungal colonization. Mucins may alter the function of individuals proteins (e.g. amylase, proline-rich proteins and statherins) or act as a bridge between bacteria (e.g. *Streptococcus mutans*) and other salivary protein [35].

Etiology and pathogenesis of dental caries

Extensive researches indicated the dental caries is the result of bacterial infection, also influenced by host and dietary factors. The multifactorial etiology and their interactions lead to disturbances in the mineralization of enamel surface of the tooth with the presence of dental plaque resulting in the formation of dental cavities.

Analysis of salivary proteins and enamel pellicle indicate that some proteins prevent the adherence of oral microorganisms to tooth surface and inhibit their growth to the extent that control predict dental caries development [36].

The role of oral cavity microflora in dental caries

More than 700 bacterial species are responsible about the complex microbial system in the oral cavity. They are essential in maintain oral health.

Any disturbance leads to negative results which may be lead to initiation of disease.

Some salivary proteins may interfere with the growth of pathogenic microbes in the oral cavity, it is important to revisit their potential role in cures, treatment or prevention [37].

Over the last few decades, extensive research in this field has provided important information about the relationship between the occurrence of tooth decay and bacterial composition in the oral cavity.

Essentially in the progress of dental caries is the fermentation by food bacteria in release of products from acidic fermentation by food bacteria in the saliva and dental plaque. In healthy subjects, the cariogenic bacteria is at a lower level under suitable conditions. The increase in consumption of carbohydrates will lead to increases the probability of dental caries development [38].

In a study by Van Houte [39], *Lactobacilli* and *S. mutans* levels were carried out (as predictors of carries-risk). He concluded that the levels are not indicators of possible caries risk but they are indicator for prediction in high-caries risk groups of individuals.

According to some authors [9], however, the type the diet is important rather than the microorganisms in dental caries and in the dental plaque.

Level of *S. mutans* in elderly patients do not correlate with the occurrence of dental caries [14], and the opposite in children with blood disorders like blood dyscrasia has been documented [40].

The adhesion of oral microbes on the surface of the tooth enamel is mandatory in order to initiate the growth of the pathogenic plaque [41,42] which is controlled by human saliva due to protein content of the pellicle layer on the enamel surface.

Acquired enamel pellicle

A non-cellular layer of specific glycoproteins is defined as acquired enamel pellicle (AEP) usually formed on oral cavity surfaces immediately after exposure to saliva. This (AEP) covering the tooth surface is the result of physical bonds between the tooth surface and molecules of proteins, peptides, lipid and carbohydrates. The thickness of the pellicle varies from 0.5 µm to 1 µm [44], making conditions suitable for the adhesion of microorganisms present in the oral cavity.

The demineralization effect of acids from non-bacterial sources is countered by the protective activity of the acquired dental pellicle [45].

The acquired enamel pellicle has binding sites specific for the oral microflora; the process of protein-microbe adhesions comprises stero-specific interactions between pellicle receptors and adhesions on the surface of microbial cells [46].

The demineralization/remineralization on the enamel coated with the natural pellicular layer is influenced by the presence of peptides and proteins binding calcium and phosphate which are parts of the pellicle [47]. Pellicle is also capable of regulating the adhesions of pathogenic microbes, as some proteins contained there *in vivo* may inhibit or accelerate the growth of oral microorganisms. These oral microorganisms usually adhere to immobilized proteins and peptides rather than to those in solution.

Enamel demineralization and remineralization

Demineralization and remineralization are essential for the maintenance of the tooth integrity. Demineralization usually happened as a result when acid coming from the plaque diffuse to the enamel crystals of the outer tooth surface. Demineralization of the enamel crystals occurs at demineralization PH 5 - 5.5 or lower, resulting in the development of dental caries. Consequently, the buffering capacity of saliva is critical for neutralizing acid, thereby preventing caries. In contrast, remineralization replaces the minerals lost during enamel demineralization.

Salivary Statherins produce a calcium and phosphate supersaturation state in saliva, which maintaining a high calcium level in saliva available for remineralization of enamel and high phosphate levels for buffering [35].

Saliva contains numerous proteins with antimicrobial properties, which are subdivided into (e.g. IgA, IgG, and IgM) and non-immunologic (e.g. proteins, peptides and enzymes). Salivary immunoglobulin is produced by immune cells within the gland in response to a foreign pathogen. Secretory IgA functions as the first line of mucosal defense and it's activity usually on mucosal surfaces where it binds microbial antigens inhibiting their attachment to oral surfaces. Other immunological molecules are scanty in saliva and coming from

crevicular fluid. IgG inhibits bacterial colonization and protect against tooth decay salivary IgE reaches the oral cavity via crevicular fluid [35].

There are many non-immunologic proteins with anti-microbial properties in saliva, such as lactoferrin, lysozyme, and peroxidase.

Most of them are coming from an acinar cells. Meanwhile lysozyme is coming from the basal cells of striated ducts in the parotid gland.

Lysozyme exhibits antibacterial activity by hydrolyzing 1,4-glycoside between N-acetylmuramic acid and N-acetyl-glucosamine in the peptidoglycans on bacterial cell walls.

Lactoferrin binds ferric iron making it unavailable as a nutrient source to microorganism which depends on iron for survival [35].

Peroxidases, salivary peroxidases and myelo peroxidase catalyze the oxidation of thiocyanate ion to generate oxidation products that inhibit the growth and metabolism of microbes.

Other non-immunologic salivary proteins with anti-microbial properties include histatins, cystatins, and glycoproteins such as salivary agglutinins. Salivary amylase, a major component of parotid saliva, begins the digestion process of starch. Similarly, fat digestion is initiated by salivary lipase [35].

Salivary proteome

Over the last decade or so, there has been an increase in the number of investigations related to identification of the protein components of saliva to improve diagnosis and monitoring of diseases. Consequently, the research for salivary biomarkers has initiated the cataloging of the human salivary proteome either from healthy individuals or from individuals with oral and systemic disease.

Initially, the studies of oralome-the oral proteome of human origin, especially the salivary proteome were carried out with the aid of the gel-based approaches.

Many types of proteins were identified by gel approach either in whole saliva or in secretion of the separate salivary glands. Stimulated saliva used as a disease biomarkers concerning Sjögren's syndrome, periodontitis or dental caries [48-50].

Salivary protein biomarkers of caries risk

Candidate protein studies

The first attempts to relate the protein composition of human saliva and caries susceptibility depend on the determination of the total protein concentration. From the survey of published trials in this field, few articles showed statistically significant differences in the total salivary protein content between CF and CA individuals [51-54].

They concluded that the total protein content was increased with caries activity [51,52,55]; however, no differences attributable to caries activity were confirmed in several experimental studies published to date [56-60].

The use of total protein concentration as a simple test susceptibility was failed. Not only the total protein concentration but also the qualitative composition of salivary proteins plays an important role.

A number of studies have also been carried out the characteristic features of salivary proteins of healthy individuals compared to salivary samples of the patients with dental caries using electrophoretic analysis.

In one study [61], the authors qualitatively analyzed protein profiles of whole unstimulated human saliva attempting to find a correlation with (DMFT).

Proteins identification according to [62-65] revealed no significant dissimilarities between men and women, and in both genders, only minimal correlation were established. Proteins composition in whole saliva was studies for subjects with the active dental caries by Roa., *et al*. [56] by comparing the individuals with filed caries cavities and the caries-free subjects.

On the other hand, in the study of caries in early childhood individuals [66], the increased number of bands of PRPs was determined and correlated significantly with entities without tooth decay according to the authors is linked with the protective effect of PRPs.

Immunoglobulins

In the last years, some of salivary proteins that have potential to be a diagnostic aids and biomarkers for dental caries have examined.

The various immunoglobulins that constitute the major group of proteins of human saliva had a great deal of attention.

The most prominent immunoglobulins in human saliva are a subclasses of A (IgA) followed by immunoglobulin G (IgG) and immunoglobulin M (IgM) subclasses. S. IgA is abundant in the mucosal secretions. It is proved to be a factor that protects against dental caries through controlling the growth of cariogenic microorganisms, preventing pathogen adhesions and the cavitation of bacterial enzymes and toxins. S. IgA is a protein responsible for adoptive immunity. According [67], such IgA mediated immunity can be induced most efficiently via the mucosal route rather than by any systemic route [67].

Numerous investigations have reported contradictory results with respect to correlation of salivary S. IgA with dental caries [68].

The analysis of S. IgA content in saliva of healthy patients, were significantly higher than in patients with caries of contact surfaces of lateral teeth, implying an effective defense function [69].

Similarly, S. IgA tends to be higher in caries free status with no statistically significant differences between rheumatoid arthritis and non- rheumatoid arthritis individuals [70].

Some authors, on the other hand, observed no change in S. IgA in group of children with diabetes mellitus [71].

Thus, the available evidence demonstrates conflicting and inclusive results regarding the IgA content in caries- active samples and caries-free controls.

Metal ions chelators

It is well known that the large group of salivary proteins represents proteins that act as metal ion chelators: lactoferrin, calgranulins, and calprotectin.

Lactoferrin which is considered as an iron binding glycoproteins is usually derived from the serous cells of the major and minor salivary glands. The role of lactoferrin in maintaining oral health is still under discussion. Lactoferrin plays an important role in bacterial colonization and agglutination inhibition of *S. mutans* by chelating the available iron, preventing bacterial adhesions and modifying the

bacterial metabolism. In case if it is alone or in combination with lysozyme a broad range of activities destructive to or inhibitory the growth of microorganisms.

There are controversial opinions, whether the levels of various salivary antimicrobial agents, especially lactoferrin are related to dental caries susceptibility. No relation was observed between caries and salivary lactoferrin in patients with insulin-dependent diabetes mellitus [72].

Calgranulin A, Calgranulin B and Calprotectin, participate in anti-inflammatory reactions, including both anti-microbial mechanisms and Th1 cell-mediated immunity [73], and have been used as a promising indicator of inflammation [74]. It's ability to react to viral and bacterial infections may lead to the possible association of this proteins in saliva with dental caries. Also, its bacteriostatic effect is a function from competition between protein and bacteria for zinc [75]. Its antimicrobial role and the relation with oral microorganism is not yet fully understood. Salivary antimicrobial proteins levels in saliva are related to individual variabilities. These levels are constant throughout the time and are associated with oral colonization of the cariogenic group of bacteria [76].

Host-defense salivary proteins

Various categories of host-defense salivary proteins are available, that can attack infectious oral microorganisms.

Lysozyme is the most well-known and powerful natural factor inhibiting the growth of bacteria by penetrating bacterial cell walls. Also it has antifungal and antiviral activities.

Lysozyme may bind, aggregate and destroy gram-positive bacteria and, to a lesser extent, gram-negative bacteria.

Lysozyme hydrolyzes the linkages in the bacterial cell wall, thus neutralizing the pathogenicity of bacteria by degrading peptidoglycans [77].

Many studies correlated caries with salivary lysozyme have been focused primarily on pre-school age children with deciduous and/or permanent dentition.

Bai., *et al*. [78] observed the possible association of an increase levels of lysozyme in both stimulated and unstimulated saliva with early childhood caries- ECC. Likewise, in a group of children suffering from severe early childhood caries - s. ECC, revealed that the salivary lysozyme level and activity were significantly increased compared with the caries-free group.

A significant reduction in counts of *Streptococcus mutans* were observed after cavity sealing may be explained by the antimicrobial activity of lysozyme.

Controversially, he fold increase in salivary lysozyme levels were observed in the caries free group compared to that of early childhood caries group. Sometimes after cavities were filled, no changes in concentrations of protein were detected.

There are some studies identifying the links between salivary histatins and caries activity. Most of the studies examined the saliva of children with mixed or permanent dentition. Researchers have shown that the salivary level of histatins-5 significantly increase in the early childhood caries group compared to the initial demineralization mild group and the control caries free group, suggesting a role of antimicrobial factors in the defense of oral infection [79].

Human salivary statherin is secreted 43 amino acid residue phosphoprotein, has a role in the formation of acquired dental pellicle. Because statherin secreted by parotid by parotid and submandibular-sublingual glands degrades rapidly its level is significantly lower in whole saliva than in glandular secretions [80].

One of the most important function of salivary statherin is its great affinity for calcium phosphate salts: statherin inhibits both primary and secondary calcium phosphates precipitation pellicle influences the enamel demineralization - remineralization by controlling the diffusion of calcium and phosphates ions. On the other hand, as a constituent part of enamel pellicle, it may inhibit the adhesion of cariogenic bacteria [81].

Cytokines

Caries pathogens can stimulate immune calls to produce cytokines that may contribute to host protection and the regulation of bacterial infection.

They are low molecular weight proteins in the form of peptide, protein and glycoprotein forms. They act in nano concentrations affecting the host immune system, producing inflammation or controlling the inflammatory process.

Salivary cytokines become a subject of interest in relation to dental caries in a relatively late period [82].

Protease inhibitors

The secretory leukocyte protease inhibitor [SLPI] is a cationic protein first found in mucous secretions. Recently, scientific researches show wide range of activity including effectiveness in killing bacteria, preventing the growth of and reproduction of fungi and viruses. It belongs to the family of proteins with immuno- modulatory and anti-inflammatory properties, which could help to protect oral health. Usually, it is present in mucous membranes and secreted by variety of epithelial cells. In high concentrations, it is released by serous cells of parotid, submandibular and submucosal glands [83-87].

The antimicrobial activities of SLPI have not been fully explained. SLPI has bactericidal and antifungal functions in acquired dental pellicle and the presence in saliva can lead to the presumption of possible participation of SLPI in the processes of caries formation.

Cystatins

Cystatins is a group of proteins present in saliva. They contain a group of evolutionarily related proteins. Their function mainly as inhibitors of cysteine proteinases, also can act independently from their inhibitory functions.

Cystatins are expressed in diverse human tissues and body fluids including saliva.

In association with statherin, they contribute to the regulation of calcium and phosphorus metabolism. Maintaining the super saturation of calcium phosphate minerals in the saliva and plaque fluid is condition for preventing the formation of enamel lesions or the progression of dental caries [88].

Bacterial agglutination and adhesion proteins

Adhesion to dental surfaces and the mucous membranes are the most important factor that influences colonization of bacteria of the oral cavity. Mucins, salivary agglutinin and fibronectin are potential salivary marker that promote bacterial agglutination and adhesions. Mucins are highly expresses in secretions of mucous acinar cells of submandibular, sublingual and minor salivary glands. Two genetically

different salivary mucins constitute the highly abundant salivary proteins. These proteins likely play a substantial role in controlling the bacterial adhesions to dental enamel, cleaning of pathogenic bacteria and form a protective layer on the hard and soft oral tissues.

One study focused on clarifying the relationship between salivary mucins levels and caries susceptibility. Different levels of salivary mucins were observed in high and low caries-risk groups of children with mixed dentition, but no differences were noticed between the group with deciduous dentition [89].

Regarding the mechanism of mucin protective effect on dental surfaces. It was demonstrated that the adhesions of *S. mutans* in the presence of sucrose can be reduced by salivary mucin [90].

In contrast it has a metabolic role in surviving of *S. mutans in vitro* [91].

Salivary agglutinin is a member of scavenger receptor cysteine-rich superfamily. It may represent an innate defense factor acting as a pattern recognition molecule [92]. Salivary agglutinin is known mainly for its agglutinating properties of cariogenic *S. mutans* [93]. Salivary agglutinin and the common salivary protein were identified as a major host derived molecules that may influence the initial colonization of pathogenic bacteria onto the tooth surface [94].

Xerostomia in individuals with Sjögren's syndrome can lead to severe and spread of dental caries followed by loss of teeth [95]. Fibronectin, belonging to the group of multifunctional glycoprotein, is essential for biofilm formation and host colonization in the oral cavity as a receptor for *Streptococcus mutans*.

Matrix metalloproteinases

Matrix metalloproteinases represent a family of multiple Zn^{2+} and Ca^{2+} dependent endopeptidase. The human MMP family includes collagenases, gelatinases, stromelysins, transmembrane and others [96].

Recent studies show the MMPs in dentin and saliva are involved in modifications of the structure of the dentine collagen matrix during the caries progression [97]. According to a recent study [98], the elevated levels of salivary collagenase correlates with manifested carious lesions. The high levels in the dentin matrix of carious teeth indicate that those proteinases can strongly affect the progression of the dental caries. They concluded that the collagen degradation will be different at different dentin depths.

Proline-rich proteins

Salivary proline-rich proteins (PRPs) constitute the heterogenous class of intrinsically unstructured proteins with a high amount proline residues. PRPs comprising approximately two-thirds of proteins secreted by human parotid gland classified as acidic basis and basic glycosylated subclasses that have different functions.

Acidic proline-rich proteins are secreted by the major salivary glands originate in the parotid, but not in the submaxillary and sublingual glands. They were discovered as molecules expressing antimicrobial function.

There involvement in caries susceptibility is dependent on the properties of the subclasses.

Meanwhile acidic proline-rich proteins are attached to dental surfaces basic types were found to bind to the cell membranes and cell walls of oral streptococci and not adhere to the dental enamel.

A detailed summary of the literature on the properties of PRPs and their possible involvement in dental caries susceptibility is provided in the review by Levine M [99].

Conclusion

The maintenance of oral health and protection from tooth erosions is the one of the most important function of human saliva. Salivary proteins play an essential role in maintaining oral health and dentition intact.

Several studies have investigated the correlation between these protein and dental caries occurrence.

Only a few studies have indicated the possibility of a relationship between a single salivary protein or group of proteins and the caries experience.

The relationship between a single protein or group of proteins and the occurrence of dental caries were mentioned in a few studies and most of these results are controversial.

As a multifunctional disease, associating caries with only one risk factors is probably not promising and a more complex association should be sought.

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