EC DENTAL SCIENCE
Review Article

Salivary Statherin - An Overview

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Abstract

Introduction: Saliva is a clear, slightly acidic fluid and contains a wide spectrum of inorganic and organic components. The complex and diverse of salivary composition plays an important role in the maintenance of oral health.

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

Methodology: The review is comprehensive research of PUBMED since the year 1979 to 2021.

Conclusion: The present review is a valiant attempt which highlights the possible potential relationship between the salivary statherin and dental caries. Recently there has been an increasing interest in identification of disease specific salivary markers with clinical relevance. Statherin could possibly play a role in dental calculus formation and another role in the defense mechanism against dental Caries. The influence of bacterial proteases and salivary flow on the statherin levels should be investigated and finally longitudinal follow-up studies to investigate the long-term influence of the statherin and other proteins related are to calcium hemostasis, like PRPs and cystains, on oral hygiene status, dental caries, erosion and dental calculus formation are required.

Keywords: *Saliva; Salivary; Statherin; Dental Caries*

Introduction

The traditional triad of host factors - the teeth, the microbes and the diet- is a simplistic representation of the complex interrelationships in oral cavity. With regard to the caries process, the quality of tooth structure and the saliva are the major host factors that should be considered. Poor tooth quality, such as hypomineralized enamel, is associated with increased rates of caries, and changes in salivary quantity and/ or quality has a profound effect on the whole oral environment, affecting caries rates, oral comfort, periodontal health and resistance to infection [1].

Saliva:

Composition,

Saliva in the mouth 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+}, $P\bar{O}_4^{-3}$ and $Hco\text{-}_3$. Saliva is supersaturated with calcium phosphates that help to prevent demineralization of the teeth. Specific phosphoproteins (Proline- rich proteins and Statherin) that inhibit the precipitation of calcium phosphate crystals from the supersaturated saliva onto the teeth, are also present. The alkalinity or acidity of saliva depends on the rate of flow but the PH is usually within range 6.2 to 8.0. There are probably around 50 different proteins in saliva, the major ones being the enzyme amylase and mucins, which are glycoproteins. Those present in smaller amounts include the enzyme Lysozyme and Sialoperoxidase, as well as Lactoferrin, Histatins and various immunoglobulins, all of which have protective functions in the mouth [2].

The importance of saliva is often over-locked, however, it has several critical roles in the caries process. Saliva is excreted from the major and minor glands at different rates and with different constituents depending on the presence or absence of stimulatory factors.

Saliva stimulated by chewing has increased calcium and phosphate ion concentration. A gustatory effect, such as that induced by some food acids, has been shown to stimulate a higher flow rate of saliva than stimulation by mechanical chewing. By removing substrate and buffering plaque acid, saliva helps to balance the caries process and has critical role in remineralization as it provides a stabilized supersaturated solution of calcium and phosphate ions as well as fluoride ions from extrinsic sources [1].

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, especially the histatins, mucins and statherins, 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 [1].

Time

When acid challenges occur repeatedly, the eventual collapse of enough enamel crystals and subsequently rods will result in surface breakdown. This may take from months to years, depending on the intensity and frequency of acid attack.

This means that, in all months there is continual demineralization of enamel; therefore, an individual is never free of dental caries [1].

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

- The composition and amount of plaque.
- Sugar consumption - especially sucrose (frequency and timing).
- Fluoride exposure.

- Salivary flow and quality.
- Enamel quality.
- Immune response.

Thus, the term caries free is best changed to the term 'caries-inactive' to more accurately reflect clinical reality [1].

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 reduced, the rate of demineralization and subsequent tooth breakdown will increase [1].

Functional properties of saliva

Saliva is a complex fluid where the various constituents act alone or in concert to perform different functions in the oral cavity. The many functions of saliva can be broadly divided into buffering action, lubrication, maintenance of tooth 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 also contribute, but mainly during unstimulated, low-flow rates. The hydrogen-binding sites of some proteins and urea add to saliva's buffering capacity.

Saliva is highly viscous, providing lubrication for efficient movement of the tongue and lips during eating, swallowing, and speech. Among the organic constituents, mucin are the most important for lubricating oral surfaces. These complex glycoproteins are found as high (MG1) and low (MG2) molecular weight mucins. Mucins have high viscosity and elasticity, strong adhesiveness, and lubricant hard and soft tissue surfaces. They also have antimicrobial activity, regulating bacterial and fungal colonization of the oral cavity. Mucin form heterotypic complexes that may alter the function of individual proteins (e.g. amylase, proline-rich proteins, and statherins) or act as bridge between bacteria (e.g. *Streptococcus mutans*) and other salivary proteins [3].

Enamel demineralization and remineralization are crucial for maintaining tooth integrity. Demineralization occurs when acid generated in the microbial plaque diffuses to the enamel crystals of the outer tooth surface. Dissolution of the enamel occurs at 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. Statherins produce a calcium and phosphate supersaturation state in saliva, which aids in the maturation and remineralization of enamel [3].

Saliva contains numerous proteins with antimicrobial properties. These proteins can be subdivided into immunologic (e.g. IgA, IgG, and IgM) and non-immunologic (e.g. proteins, peptides, and enzymes). Salivary secretory immunoglobulin A (IgA) is produced by immune cells within the gland in response to a foreign pathogen. Secretory IgA functions as the first line of mucosal defense. It is active on mucosal surfaces where it binds bacterial antigens, inhibiting their attachment to oral surfaces. In contrast to IgA, other immunological molecules are present in relatively low amounts in saliva and are primarily derived from gingival crevicular fluid. IgG inhibits bacterial colonization and protects against tooth decay. Salivary IgE reaches the oral cavity via crevicular fluid along with contributions from intraepithelial mast cells in atopic and allergic conditions [3].

There are many non-immunologic proteins with antimicrobial properties in saliva, such as lactoferrin, lysozyme, and peroxidase. Most of these proteins are derived from salivary gland acinar cells. However, lysozyme is derived from basal cells of striated ducts in the parotid gland. Lysozyme exhibits antibacterial activity by hydrolyzing 1,4-glycoside between N-acetylmuramine acid and N-acetyl-d glucosamine in the peptidoglycans on bacterial cell walls. Lactoferrin binds ferric iron, making it unavailable as a nutrient source to microbes that rely on iron for their survival. Peroxidases, salivary peroxidases, and myeloperoxidase catalyze the oxidation of thiocyanate ion to generate oxidation products that inhibit the growth and metabolism of microbes. Other non-immunologic salivary proteins with antimicrobial 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 lipases [3].

Statherin is a protein in humans that is encoded, by the STaTH gene [4,5]. It prevents the precipitation of calcium phosphate in saliva, maintaining a high calcium level in saliva available for remineralization of tooth enamel and high phosphate levels for buffering [6].

The statherin-inspired and elastin like recombinases (ELRS) have the ability to induce and control growth of minerals on the biofunctional surfaces [7].

("Biomineralization and Biomaterials, 2016. R.A. GiaCaman, ... C.A. Carrera").

Following the maturation stage, where most of the enamel minerals content is acquired, the final mineralization is completed after eruption (Dirks, 1966; Rabinson, 2014).

In this nonameloblast-controlled stage, interaction with saliva contributes a posteruptive maturation of the enamel surface via diffusion of ions such as calcium, phosphorus, magnesium, fluoride and potentially other components (Briner., *et al*. 1971; Mandel, 1987). Almost immediately after eruption enamel is covered by an acellular Layer of protective HAP-binding salivary proteins (e.g. Proline-rich proteins, mucinous proteins, and statherin) called acquired enamel pellicle (AEP) that directly contributes to the posteruptive maturation of enamel (Hannig., *et al*. 2004).

It has been reported that statherin may function, in the transport of calcium and phosphate during secretion in the salivary glands (Bennik., *et al*. 1981; Schlesinger and Hay, 1977).

In saturated solutions of calcium phosphate minerals, statherin inhibits spontaneous precipitation and crystal growth, providing a protective and reparative but stable environment for the teeth (Hayel., *et al*. 1984; Johnsson., *et al*. 1991).

Acting together with the acidic Proline-rich and mucinous proteins, statherin maintains the supersaturated state of saliva with respect to most calcium phosphate salts in the AEP, a condition needed for the recalcification and stabilization of the tooth enamel and for the inhibition of formation of mineral accretion on tooth surfaces (Raj., *et al*. 1992).

In this environment, enamel mineralization is completed by replacing more acid-soluble HAP (e.g. carbonate- substituted HAP) with more acid-resistant HAP (e.g. fluorapatite).

After this process, the porosity and permeability of the 200 μm outer enamel layer is greatly reduced. (Garcia-Godoy and Hicks, 2008).

It is important to take into consideration that AEP also contributes to bacterial adhesion, favoring demineralization, and subsequent caries development.

For more details on the dynamics of the cariogenic bacterial biofilm, the reader is referred to specific caries Literature (Nyvad., *et al*. 2013).

In 1992, M Hany., *et al*. investigated the role of salivary statherin in dental caries. They measured salivary statherin levels in both male and female groups divided equally into 3 age subgroups, the first one for young adults, the second one for the middle age and the third one for the old age. Also, all of these subgroups are monitored in both caries active group and another caries inactive group (Control group). There was no statistically significant differences of salivary statherin concentrations between male and female groups.

They found salivary statherin level was higher in middle age male group with caries-inactive group.

They concluded the salivary statherin play an important role in protection of teeth against dental caries, and they recommended more research work and more investigations towards its mechanism and mode of action and its importance as a defense barrier against dental caries [8].

Yavgil' dina DA; Saleev RA examined the influence of statherin on the rate of dental diseases and determined the concentration of salivary statherin in patients with dental caries. They found statherin saliva level was higher in patients with dental caries and its complications compared to healthy controls. Mean saliva statherin concentration was Me = 6.1 [2.5, 18.4] mmol/1 in patients with caries compared to Me = 3.5 [2.9, 7.3] mmol/l in control group.There was no statistically significant differences of saliva statherin concentrations between men and Women in both groups. Oral hygiene (as defined by simplified and hygiene index), food Consumption (right after a meal or 4 hours after a meal), bad habits (smoking had no effect on statherin concentrations in saliva) [9].

They concluded that the statherin saliva levels are indicative of the diseases of the oral cavity "Kazon medical journal 95 (5), 1654 657, 2014.

Harish Devarajan, Sujatha Soma Sundaram reviewed the relationship between salivary proteins and dental caries. Dental caries is a common disease process that affects large proportion of the child population worldwide

Extensive research in the past indicates that it is the past indicates that it is the result of bacterial infection, also influenced by host and dietary factors. The current caries research seeks to identify risk factors as well as natural oral defenses that may protect against or prevent caries development, in spite of being the strongest defense system, still has a wide array of properties and proteins whose role is yet not clear known.

Saliva is essential for a life long conservation of the dentition. Various functions of saliva are implicated in the maintenance of oral health and the protection of our teeth:

1. The tooth surface is continuously protected against wear by a film of salivary mucins and proline rich glycoprotein.
2. The early pellicle proteins, proline-rich proteins, and Statherin promote remineralization of the enamel by attracting calcium ions.
3. Demineralization is retarded by the pellicle proteins, in concert with calcium and phosphate ions in saliva and in the plaque fluid.
4. Several salivary glycoproteins prevent the adherence of the oral microorganisms to the enamel pellicle and inhibit their growth.
5. The Salivary bicarbonate/carbonate buffer system is responsible for rapid neutralization of acids.

They summarized the relationship between dental Caries and tooth protective salivary proteins with their potential as functional biomarkers, for caries risk assessment. "Drug Invention Today 11 (6), 2019 [10].

In 2017, Deepak Gowda Sadashivappa Pateel., *et al*. correlate in a preliminary study the salivary statherin and calcium levels with dental calculus formation.

As saliva is essential for life long maintenance of oral health, it is composed of a variety of electrolytes, immunoglobulins, proteins and enzymes and plays some important functions in the maintenance of oral heath such as Lubrication of the oral mucosa defense from infections, protection against demineralization [11].

The four major Salivary Proteins, that is, statherin, the acidic PRPS, cystatins, and histatins, are primarily responsible for the maintenance of the homeostasis of the supersaturated state of saliva with respect to calcium phosphate salts. Statherin is a very potent inhibitor of crystal growth in exhibit unusually high affinities for hydroxyapatite.

It is a multifunctional peptide that possesses a high affinity for calcium phosphate minerals, maintains the appropriate mineral solution dynamics of enamel, promotes selective initial bacterial colonization of enamel, and function as a boundary lubricant on the enamel surface. Statherin inhibits both nucleation and growth of hydroxyapatite crystal and its concentration.

It is the only salivary protein that inhibits the spontaneous precipitation of calcium phosphate salts from the supersaturated saliva. It inhibits primary as well as secondary precipitation of calcium phosphate salts [12].

In addition, Statherin may function in the transport of calcium and phosphate during secretion of salivary glands. Statherin concentration is not subject to circadian rhythms unlike other salivary peptides [13].

Besides that, statherin promotes bacterial adhesion to enamel surfaces, although weakly compared with other salivary macromolecules [14] and acts as boundary lubricant at the enamel interface [15].

The aim of the present study was to estimate and correlate salivary statherin and calcium concentration to dental calculus formation.

The present study was a valiant attempt which highlights the possible potential relationship between the salivary statherin and dental calculus. They concluded the following observations:

1. Salivary statherin levels differ significantly with different grades of calculus.
2. Salivary statherin is inversely proportional to the calculus deposition.

Statherin could possibly play a role in the formation of dental calculus [16].

In 2021 Deepak Gowda Sadashivappa Poteel., *et al*. investigated the association of salivary Statherin, acidic proline-rich proteins (PRP) and calcium on oral hygiene.

Saliva is composed of a variety of electrolytes, exosomes, micro RNA, and cytokines, which are crucial biomarkers in the detection of oral and systemic diseases [17].

As of today, saliva finds a wide range of applications including HTV testing [18], renal disease monitoring [19], chronic Kidney disease [20], Cardiovascular risk management [21], Viral diagnosis [22], forensic medicine drug abuse monitoring [23], Alzheimer's disease [24], Psoriasis [25], stroke [26] and dental studies mainly related to periodontal health and dental caries [27].

Taking into account the results of these studies and other demonstrated protective functions of statherin may imply that statherin concentration in saliva could possibly influenced by the oral hygiene status of the individual and emphasize their protective role in the maintenance of oral health.

This study investigated the association between the salivary statherin, a PRP, and calcium with oral hygiene status. Poor oral hygiene was associated with increased salivary statherin and reduced "PRP levels [28].

Conclusion

The present review is a valiant attempt which highlights the possible potential relationship between the salivary statherin and dental caries. Recently there has been an increasing interest in identification of disease specific salivary markers with clinical relevance. Statherin could possibly play a role in dental calculus formation and another role in the defense mechanism against dental caries. The influence of bacterial proteases and salivary flow on the statherin levels should be investigated and finally longitudinal follow-up studies to investigate the long-term influence of the statherin and other proteins related are to calcium hemostasis, like PRPs and cystains, on oral hygiene status, dental caries, erosion and dental calculus formation are required.

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