Review article

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"THE SALIVARY BIOMARKERS FOR DENTAL CARIES DIAGNOSIS - A REVIEW"

Dental Science

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ABSTRACT

Dental caries is the most prevalent and chronic oral disease affecting children and adults around the world. Irrespective of its high prevalence rate the proper aid of diagnosing high risk caries risk individuals are still lacking. Saliva can be used to study the physiological state of the body, having the potential to be used in the early detection and diagnosis of diseases. This is due to the abundant protein content in saliva, which can behave as biomarkers for diseases. There are various proteins candidate for a biomarker role on dental caries, namely, soluble immunoglobulin A, mucins, cystatin, statherins, defensins and CD14 aid in the early diagnosis of the disease susceptible individuals.

KEYWORDS

Introduction:

Dental caries is the most prevalent chronic disease around the world [1]. The fermentation of dietary sugars by the acid producing micro-organisms inhabiting in the oral cavity initiates the carious lesions on the tooth structures [2]. Though, the carious lesion initiation is by micro-organisms, the etiology of dental caries is a multi-factorial [3]. Apart from the micro-organisms, both human related factors such as immune competence, saliva buffering capacity, and external environmental factors such as diet, oral hygiene maintenance, or fluoride exposure have a significant impact on dental caries progression [4].

Despite its high prevalence rate and its direct and indirect impact on human health, there are still no effective diagnostic tools to predict dental caries. Though various diagnostic tests are developed to diagnose the developing carious lesions, an appropriative method was not developed to identify before the initiation of the carious lesions. In such a context, the diagnostic applications of saliva in the diseases oral cavity and systemic health gained the importance.

Saliva is the easily available and accessible body fluid, and the markers expressed in saliva can be used for the diagnosis of different diseases, including cancer, diabetes, hereditary disorders, and infections [5].

The saliva also contains many molecules that can directly or indirectly influence oral micro-organisms and their potential cariogenic effect, and thus measuring the levels of appropriate salivary compounds may provide information to predict caries risk of the individuals [6].

The saliva also controls the natural protective mechanism of the dental caries process in the oral cavity [7]. The salivary pH, the acid-neutralizing power, and the calcium, fluoride, and phosphorus content of the saliva aid in the natural buffering action of the saliva. It was also proved that the rate of flow and the viscosity of saliva influence the initiation and development of dental caries. In addition, the protein components of the saliva aid in diagnosis of the various systemic and oral health diseases [8,9]. Thus, the present review aims to analyses and discuss the various diagnostic components of salivary proteins in dental caries.

Role of salivary proteins:

Human salivary secretions are supersaturated with calcium and phosphate, but spontaneous precipitation from saliva to tooth enamel does not occur normally. This unexpected stability is mediated by salivary proteins, namely, statherin, acidic prolein rich proteins (PRPs) cystatins, and histatins. The protective role of these proteins differ from other salivary host defence proteins by having a specific function only restricted to the oral environment, i.e., the maintenance of the homeostasis of the supersaturated state of saliva. In addition, these proteins are multifunctional in that they are also partly responsible for the remineralization capacity of saliva [10].

Statherins are the only identified inhibitor of primary precipitation in saliva, and it is a very potent inhibitor of crystal growth [10]. The statherins present in stimulated saliva are sufficient to inhibit the precipitation of calcium and phosphate salts effectively. The acidic proline-rich proteins (PRPs) account for around 25- 30% of all proteins in saliva, and they have high affinity for hydroxyapatite crystals. The acidic PRPs binds to the free calcium, adsorb to the hydroxyapatite surfaces, and in turn inhibit the enamel crystal growth, and regulate hydroxyapatite crystal structure. The multifunctional properties of acidic PRPs, like statherins, are shown by their capacity to promote the attachment of bacteria to apatitic surfaces of the tooth structure [11].

Cystatins form a family of cystein containing phosphoproteins, which play a minor role in the regulation of calcium homeostasis in saliva. Phosphorylated and non-phosphorylated cystatins bind to hydroxyapatite crystals, but the protective role of cystatins in the caries process is unclear [10]. The scientific evidence showing the correlation between the above-described proteins and dental caries are very sparce. The fact that, statherin, acidic PRPs, and cysteins plays an important role in the protective and reparative systems which is essential for the integrity of the teeth is very obvious [10,11].

Role of Bacteria-aggregating Proteins:

The acquired enamel pellicle is a very thin film consisting mainly of salivary proteins specifically absorbed to the surface of the enamel. The surface pellicle protects the enamel dissolution from the acids produced by the acidogenic bacteria. The diffusion fluxes are reduced by the presence of pellicle, leading to a reduced demineralization potential of the bacterial acids [12].

Several proteins like agglutinins, α-amylases, statherins, mucins, acidic PRPs, and immunoglobulins are reported to bind with oral streptococci [10]. These proteins are also present in the salivary pellicle, and therefore they tend to mediate the specific adhesion of bacteria to tooth surfaces. The parotid salivary agglutinins and similar proteins found in sub-mandibular sublingual saliva, are the most

significant salivary proteins in promoting the adhesion of Streptoco ccus mutans [13].

On the other hand, when these proteins exist in the liquid phase, they tend to promote bacterial aggregation and result in the clearance of bacteria from the oral cavity. The two most abundant and important agglutinins in saliva are high molecular weight agglutinin from parotid saliva and mucins. Of the mucins, the low molecular weight form, MG2, is more efficient and effective in bacterial aggregation and clearance than the high molecular weight form, MG1 [12,13].

Role of salivary Defensins:

Saliva contains various antimicrobial peptides important for the innate immunity, namely the defensins. Defensins are small, cationic proteins which have the potential antimicrobial activity. Defensins can be divided in two major subfamilies, including α-defensins and β-defensins. Both, the α-defensins (human neutrophil defensins - HNP) -1,-2,-3,-4 and the human β-defensins (HBD) -1,-2, -3, -4) are detected in salivary secretions. The bacterial charge is a significant 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 viruses [14].

Role of soluble CD14:

CD14 is a protein involved in innate immunity that acts as a receptor of lipopolysaccharide (LPS) or peptidoglycan (PGN) of gram-negative and gram-positive bacteria, respectively. CD14 is expressed on the cell surfaces of monocytes, macrophages and neutrophils, via a glycosyl phosphatidylinositol anchor, and is present in plasma as a soluble form, sCD14. Major salivary glands secrete sCD14 into the saliva and it acts as an important anti-cariogenic factor. It enables the binding between the surfaces of epithelial cells and bacteria and further activates the production of cytokines for the recruitment of phagocytes. An inverse relationship is observed between the presence of sCD14 in salivary secretions and caries initiation. Thus, the proteins sCD14 plays an important role in diagnosing and prevention of dental caries, if used as biomarkers [15].

Role of Innate defence factors:

The innate defence factors identified in saliva have been extensively studied in laboratory studies and observed that they express different antimicrobial properties. The scientific evidence obtained so far are mainly from in vitro studies, and there is only a very limited information on how these factors act in vivo. The main oral innate defense factors are the peroxidase systems, lysozymes, lactoferrins, and histatins. In laboratory studies, these proteins limit bacterial or fungal growth, interfere with bacterial glucose uptake, glucose metabolism, promote aggregation and thus the elimination of the bacteria. The salivary innate defence factors affect cariogenic bacteria such as mutans streptococci, lactobacilli, and fungi in vitro, the observations in most studies has been an inverse relationship between caries and the amounts of antimicrobial components in the saliva [16].

Role of specific defense factors:

The immunoglobulins (IgG, IgM, IgA, and secretory IgA) form the basis of the specific salivary defence against oral microbial flora. The formation of specific IgAs in saliva correlates with the colonization of bacteria in the oral cavity of caries susceptible individuals. In the oral cavity, immunoglobulins act by neutralizing various microbial virulence factors, restricting the microbial adherence, and agglutin ating the bacteria, as well as by preventing the penetration of foreign antigens into the oral mucosa. Immunoglobulins are also capable of opsonizing bacteria for phagocytes, which are reported to remain active in dental plaque and saliva. The role of salivary Igs in dental caries initiation and progression is still a matter of debate [17].

Conclusion:

The dental caries significantly affect the salivary proteome and aid in the early diagnosis of the disease susceptible individuals. The saliva appears to be a potential source of biomarkers for dental caries identification in children and adults. The various proteins candidate for a biomarker role of dental caries, namely statherin, acidic prolein rich proteins (PRPs) cystatins, histatins, agglutinins, mucins, defensins, CD14, and defensins aid in the diagnostic applications of saliva in dental caries.

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