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Review Article

The role of saliva in maintaining oral health: Aid to diagnose systemic ailments-A review

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ABSTRACT

Saliva is a complex secretion from three major and various minor salivary glands present in mouth. From clinical point of view saliva is an ideal diagnostic fluid because it is non-invasive fluid and can be easily be collected from the patients for biochemical analysis. The other significant characteristic pertinent to saliva is the handling procedure which is much simpler in comparison with serum or blood. There is plethora of studies which shows a positive correlation between blood biomarkers and salivary biomarkers in different clinical conditions of oral and systemic diseases. Saliva has an important role in maintain oral health through variety of its secretions like calcium, phosphorus, Bacteriocins, salivary leukocyte protease inhibitors different enzymes like ptyalin, amylase for carbohydrate and protein metabolism which maintains tooth integrity when there is demineralization and also acts as first line defense against various bacterial and viral infections. In 21st century endodontic there is a paradigm shift in research on the change in composition of the saliva and biomarkers in presence of periodontal / pulpal and other systemic diseases. Molecular methods for identification and quantification of salivary biomarkers like IL-6, IL-8, MMPs are available at chair side for rapid diagnosis of various inflammatory or infective etiology of oral diseases.

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1. Introduction:

Saliva is a complex secretion secreted by three pairs of large major salivary gland and various minor salivary glands in the oral cavity.¹ About 93% of salivary volume is secreted by the major salivary glands and the remaining 7% by the minor salivary glands located in various region of the oral cavity.² The salivary glands are made up of acinar and ductal cells and secretion differs in composition between major and minor salivary glands. Parotid gland secretion is largely serous in nature and is produced by

acinar cells. one important characteristic of parotid gland is that an enzyme called alpha amylase is synthesized in large quantity in comparison to other major, minor salivary glands. The secretions of parotid gland also contain less amount of calcium in comparison to others major and minor salivary glands. On the other hand the mucins which are mainly produced by the submandibular and sublingual glands where as proline and histatin rich proteins are produced by the parotid and submandibular glands.² The average daily secretion of human saliva is 1.5 liters per day. All Salivary glands are under control of autonomic nervous system (ANS). At rest, the salivary secretion ranges from 0.20 to 0.40 ml/min and is mostly produced by major

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salivary gland except parotid glands. On stimulation through mechanical means secretion rate of saliva may increase to a maximum of 1.5 ml/min. saliva productions follows circadian pattern which indicate that the greatest volume of saliva is produced during and after meals and falls considerably and approaches zero at night during sleep. The composition of saliva contains 99% of water and the other 1% of organic and inorganic molecules.³ Human Saliva can indicate the plasma levels of drugs, hormones, chemokine's, enzymes and other biomarkers like IL, MMPs, DNA, RNA and other expressed proteins. Hence it is non-invasive and can be a good indicator for measuring various concentrations of substances in comparisons to plasma.

2. Clinical Importance of the Quantity and Quality of Saliva in Maintaining Oral Health

In various clinical conditions like prolonged use of antihypertensive, antihistaminic, antipsychotic drugs the secretions of saliva gets reduced which is known as Hyposalivation. The others diseases like sicca dolorosa, post radiotherapy also results in diminution of salivary secretions which can affects the quality of life with increased morbidity of the patients. Hyposalivation is also known 'dry mouth' or xerostomia, which is characterized by frequent thirst, dysphasia, mucositis etc.⁴ In the oral cavity the frequently encountered signs include dry, cracked oral mucosa, fissured tongue with loss of taste sensation increase with increased frequency of fungal and bacterial infections including dental caries.² The diagnosis is purely based on clinical examinations and symptoms of the patients. Salivary gland hypo function can be quantitatively determined by sialometry. The other medical conditions like Sicca syndrome, idiopathic fibrosis of major salivary gland requires adjunct diagnostic aids like MRI, and biopsy.⁵ Just opposite to hypo-salivation there may be clinical conditions in which there is increase in secretions of saliva; this is known as hyper salivation or sialorrhea.⁶ The diagnosis is purely based on clinical examinations and symptoms of the patients.

3. Main Causes of Hypo and Hypersalivation

Salivary secretion is reduced in wide varieties of physiological conditions like age, gender, BMI and day time as it follows circadian patterns.⁵ There is diminution of salivary secretions as age advances so geriatric patients have less amount of salivary secretions in comparisons to Youngers patients. Plethora of medications has direct effects on salivary gland resulting in its dysfunction most commonly characterized by hypo-salivation.³ Certain neurological disorders like epilepsy, Parkinson's and various tumors results in hyper salivation. Heavy metal poisoning by lead, bismuth, mercury, silver, gold or arsenic can results in decreased production of saliva. Chronic

kidney diseases induced uremia, Hyperparathyroidism, brachytherapy, induced fibrosis in manor salivary gland can cause decreased in salivary gland function resulting in hypo salivation which can be irreversible. In autoimmune diseases like Sjogren's syndrome there is vascular or neurological alterations which may be alter saliva production. Other clinical conditions like hypertension, bipolar disorders, diabetes, etc., can cause hyposalivation. Physiological cause of increased saliva production occurs during tooth eruption, first trimester of pregnancy, menstruations etc. The other cause which may be pathological includes foreign body in mouth in form of complete /removal partial dentures.

4. The role of Saliva in Caries Protection

There is multiple studies which relates the compositions of saliva to the presence or absence of caries. A common method for assessing caries is through DMFT index which is characterized by decayed, missing, filled and treated. The saliva from caries free individuals have low count of antibacterial, antiviral and other expressed protein in comparison to saliva of individual having dental caries.

5. Buffering Capacity of Saliva

Salivary buffer mechanisms include calcium, bicarbonate, phosphate and some proteins like statherin have a buffer effect and also provide lactoferrin, Bacteriocins, salivary leukocytes protease inhibitors which eliminates bacterial and viral infections and remineralizes tooth structures once critical Ph is 5.5 is reached. The phosphate buffer plays an important role when salivary flow is low. At a pH greater than 6 the saliva is supersaturated with phosphate with regard to hydroxyapatite (HA). When the pH falls below the critical level (5.5) the HA begins to dissolve, freeing phosphates that attempt to restore the pH balance. In the final analysis, this depends on the phosphate and calcium ion content of the surrounding medium. Certain proteins, like sialin, or histatin and other proteins and ammonia which makes oral ecosystem alkaline, hence demineralization of tooth structures is prevented.⁷

6. Balance Between Remineralization and Demineralization

Caries is a microbial infection characterized by demineralization of inorganic components and followed by destructions of organic components. It is a sub-surface demineralization of the enamel that is covered by a well mineralized layer.² The factors that regulate the hydroxyapatite (HA) balance are the pH and the concentration of free calcium, phosphate and fluoride ions. Both the saliva and the extra cellular plaque are supersaturated with calcium, phosphate and hydroxylions with regard to HA.³ Proline-rich proteins, statherins, histatins and cystatins act in this way, while the action of

some bacterial proteases and of salivary callicrein affects these regulatory processes. There is abundance of Calcium ions in unstimulated than in stimulated saliva as its main source is the saliva secreted by the parotid, submandibular and sublingual glands, whereas when stimulation occurs the parotid gland produces the greatest volume of salivary secretion. The phosphate ions concentration in saliva from the submandibular glands is 33.33 percent in comparisons to parotid saliva.⁷ Initiation of dental caries begins when bacteria (*Streptococcus mutans*, *Lactobacilli*, *Actinomyces*) ferment carbohydrates, resulting in the formation of organic acids resulting lower pH of the saliva and the plaque. In the dynamic balance of the caries process, supersaturation of the saliva provides a barrier to demineralization and tips the balance towards remineralization. The presence of fluoride assists this balance. Also, some proteins are able to bind to the HA and inhibit the spontaneous precipitation of calcium and phosphate, thus maintaining the integrity of the enamel crystals.

7. Antimicrobial Actions

Saliva contains leukotoxins, and opsonins. The concentration of immunoglobulins Ig-A, is 3 % in comparisons to plasma which impart antimicrobial actions of saliva. The other proteins like Proline-rich proteins, Lysozyme, Lactoferrin, Peroxidases, Agglutinins and Histidine, Secretory immunoglobulin A, G and M⁸ maintains homeostatic balance of oral environment.

8. Salivary Biomarkers for Systemic Disease

Salivary composition changes in wide variety of systemic and oral diseases. In presence of periodontal, pulp and other oral and systemic diseases salivary biomarkers knowledge has become the point of care. Due to the development of laboratory nanotechnology various proteins expressed in saliva, signal molecules, hormones, and many other substances can be ascertained easily and diseases can be identified.^{3–5} Most metabolites, cytokines, signal molecules, or hormones move in a certain amount by passive filtration into saliva and their levels in saliva reflect their levels in plasma.⁸ Therefore, detection of these molecules in saliva is only a matter of the detection limits of new analytical methods. The potential of saliva as a biomarker fluid has been transformed by the development of highly sensitive proteomic analysis, which has identified the presence of over 3,000 proteins, approximately 30% of which are shared with plasma.⁹ It is also important to mention that an advantage of using saliva, as a diagnostic material, is that it can be obtained for laboratory tests noninvasively and repeatedly.⁷ Enzymes, specific and nonspecific proteins, antibodies, and other substances are among the potential salivary biomarkers of periodontal and certain distant tissue diseases. And

so saliva became the topic of interest among experts in proteomics, research of sequential composition of individual proteins. C-reactive protein is a long known indicator of inflammatory or rheumatic activity; CRP levels in plasma and saliva correlate. During periodontitis, salivary CRP levels increase and its decrease indicates a successful anti-inflammatory treatment. High CRP levels in saliva during diffuse periodontitis are a marker of local process risk for the formation or progression of cardiovascular disease with risk coefficient OR 5.6^{7,8} CRP levels increase subsequently with the severity of the periodontal disease. Literature has been published on the importance of salivary biomarkers in the diagnosis of CVDs, which includes MB (CK-MB, Myoglobin (MYO), Cardiac troponin I (cTnI), Creatine phosphokinase), Myeloperoxidase (MPO), brain natriuretic peptide (NT-proBNP), Exosomal miRNA, C-Reactive Protein (CRP), Matrix metalloproteinase-8 (MMP-8), MMP-9 and tissue inhibitor of MMP-8 (TIMP-1).^{1,3,5,10} Myoglobin, which appears in both serum and saliva bio-fluids, can be used to detect AMI. Miller and his coworkers conducted research, and established that salivary myoglobin levels were greater within 48 h of the onset of angina in AMI patients.⁴ It was proved that the unstimulated saliva concentration of Cardiac troponin-I (cTnI) at the onset of 12 h and 24 h of Acute Myocardial Infection and creatine phosphokinase-MB (CK-MB) increased in patients with AMI compared to Non-AMI controls. This study also proved the strong link between levels of serum and salivary CK-MB and CPK, indicating that saliva-based tests may provide an easy and convenient way of providing point-of-care testing of CVDs.

9. Conclusion

Saliva maintains the integrity of the oral structure, helps in the digestion and in controlling of oral infections. because of bacteriocins and other immunomodulators. Saliva plays in protecting teeth from caries by diluting and eliminating sugars and other substances, buffering capacity, balancing demineralisation / remineralisation and antimicrobial action. Saliva is also a promising option for diagnosing certain disorders and monitoring the evolution of certain pathologies or the dosage of medicines or drugs. Its advantages as a diagnostic tool include it is non invasive, easy to obtain and the positive correlation between many parameters in serum and saliva. Hence saliva can be used for diagnosing various systemic illness.

10. Authors' Contribution

Dr. Navin Mishra, Writing the article, Literature search. Dr. Md. Jawed Iqbal, Analysis and interpretation of the data. Dr. Sheeri Sabir, Conception and design; Dr. Priyankar Singh; Writing the article; Dr. Nimmi Singh, Critical revision of the article; Professor. Dr. A.K. Sharma, Administrative,

technical, or logistic support

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12. Conflict of Interest

None.

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