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Review Article

An insight into the science behind saliva and its crucial role in oral health

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ABSTRACT

Saliva, a clear, tasteless, odourless, slightly acidic viscous extracellular fluid produced and secreted by salivary glands makes the oral cavity moist ; and has very important role is maintaining the well being of the mouth. Knowledge of the salivary system and saliva is essential for evaluating prosthodontic problems and for educating patients.

1. Introduction

Saliva is a complex fluid composed of secretions from salivary glands and gingival crevicular fluid. The oral cavity is a moist environment; a film of fluid called saliva constantly coats its inner surface and occupies its space between the lining oral mucosa and teeth, thus maintaining the well being of the mouth. Saliva plays a critical role in the maintenance of oral and dental health.

2. Functions of Saliva

2.1. Taste

The Saliva formed inside the acini is isotonic with respect to plasma and as it runs through the network of ducts, where it becomes hypotonic. The hypotonicity of saliva and its capacity to provide the dissolution of substances allows the gustatory buds to perceive different flavors.

A salivary protein called Gustin is necessary for the growth and maturation of the gustatory buds.[1]Protection and Lubrication

2.2. Protection and lubrication

Saliva forms a seromucosal covering that lubricates and protects the oral tissues against irritating agents. Proteins with high carbohydrate content like mucins are responsible for lubrication, protection against dehydration, and maintenance of salivary viscoelasticity. Mucins selectively modulate the adhesion of microorganisms to the oral tissue surfaces, which contributes to the control of bacterial and fungal colonization. Mucins protect tissues against proteolytic attacks by microorganisms. Mucins also aids in Mastication, speech, and deglutition.[1]

2.3. Buffer capacity

Saliva neutralizes and cleans the acids produced by acidogenic microorganisms and thus aids in preventing enamel demineralization. A Salivary peptide called sialin helps in increasing the biofilm pH after exposure to fermentable carbohydrates. Urea is a buffer present in total salivary fluid which is a product of aminoacid and protein catabolism that causes a rapid increase in biofilm pH by releasing ammonia and carbon dioxide when hydrolyzed by bacterial ureases. The carbonic acid-bicarbonate system is an important buffer in stimulated saliva, while in

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unstimulated saliva carbonic acid-bicarbonate system serves as the phosphate buffer system. [1]

2.4. Integrity of Tooth Enamel

Saliva plays a fundamental role in maintaining the physical-chemical integrity of tooth enamel by modulating remineralization and demineralization. Active concentrations free of calcium, phosphate, and fluoride in solution and the salivary pH are the main factors controlling the stability of enamel hydroxyapatite. [1]

The presence of fluoride in saliva at low level is responsible for the stability of dental minerals and is dependent on the fluoride in the environment, especially in drinking water. [1]

Secretory immunoglobulin A (IgA) is the largest immunologic component of saliva. IgA can neutralize viruses, bacterial, and enzyme toxins. It serves as an antibody for bacterial antigens and is able to aggregate bacteria, inhibiting their adherence to oral tissues. [1]

Among the non-immunologic salivary protein components, there are enzymes like lysozyme, lactoferrin, and peroxidase), mucin glycoproteins, agglutinins, histatins, proline-rich proteins, statherins, and cystatins.

2.5. Lysozyme

Lysozyme can hydrolyze the cellular wall of some bacteria, as it is strongly cationic, it can activate the bacterial "autolisines" which are able to destroy bacterial cell wall components. [1]

2.6. Lactoferrin

Lactoferrin binds to free iron in the saliva causing bactericidal or bacteriostatic effects on various microorganisms requiring iron for their survival such as the Streptococcus mutans group. Lactoferrin provides fungicidal, antiviral, anti-inflammatory, and also serves immunomodulatory functions. [1] sialoperoxidasehypothiocyanate, a potent antibacterial substance. [1]

2.7. Peroxidase or sialoperoxidase

Peroxidase or sialoperoxidase offers antimicrobial activity because it serves as a catalyst for the oxidation of the salivary thiocyanate ion by hydrogen peroxide into hypothiocyanate, a potent antibacterial substance. [11]

2.8. Proline-rich proteins and statherins

The proline-rich proteins and statherins inhibit the spontaneous precipitation of calcium phosphate salts and the growth of hydroxyapatite crystals on the tooth surface, preventing the formation of salivary and dental calculus. Proline-rich proteins also has the capacity to selectively mediate bacterial adhesion to tooth surfaces. [1]

2.9. Cystatins

Due to the proteinase inhibiting properties of cystatins helps in controlling the proteolytic activity. [1]

2.10. Histatins

The histatins belongs to a family of histidine-rich peptides. Histatins has an antimicrobial activity against some strains of Streptococcus mutans and inhibit hemoagglutination of the periopathogen Porphyromonas gingivallis. Histatins neutralize the lipopolysaccharides of the external membranes of Gram-negative bacteria and are potent inhibitors of Candida albicans growth and development. [1]

2.11. Salivary agglutinin

Salivary agglutinin is a highly glycosylated protein associated with other salivary proteins and with secretory IgA and is one of the main salivary components that is responsible for bacteria agglutination. [1]

2.12. Salivary biomarkers

Biomarker is a biological indicator of normal or pathogenic processes.

Saliva is a useful diagnostic tool for the detection of biomarker involved with oral and systemic diseases, since it reflects the pathophysiological conditions of the organism and allows early, rapid, practical and noninvasive detection of biomarkers.

3. Salivary Transcriptomic Biomarkers

Messenger (m) RNA is the direct precursor of proteins and in general the corresponding levels are correlated in cells and tissue samples. At present, the main strategy to identify salivary transcriptomic biomarkers is through microarray technology. After profiling the transcriptomic biomarkers by microarray, they are validated by quantitative PCR (Polymerase Chain Reaction), the gold standard for quantification of nucleic acids. [2]

3.1. Exosomes

Exosomes are small, right-side out cell-secreted vesicles of about 30–100 nm, derived from fusion of multi vesicular bodies to plasma membranes. Salivary mRNA are localized inside salivary exosomes and these nucleic acids are protected against ribonucleases in saliva. Saliva exosomes have been discovered to regulate the cell-cell environment by altering their gene expression allowing us to better understand the molecular basis of oral diseases. [2]

3.2. Salivary micro RNA

MicroRNAs (miRNAs) are encoded by genes but are not translated into proteins. MicroRNAs serve important functions such as cell growth, differentiation, apoptosis, stress and immune response as well as glucose secretion. Proteins, mRNAs and microRNAs before and after pharmacological interventions provides an important information on drug efficacy and toxicity in the context for therapeutic responsiveness.[2]

3.3. Salivary gland dysfunction

1. Salivary gland dysfunction is defined as any quantitative and / or qualitative change in the output of saliva.
2. Thus salivary gland dysfunction includes either an increase in salivary output (hyperfunction) or a decrease (hypofunction).[3]

Hyposalivation: Refers to a measurable decrease in function of one or more salivary glands as reflected in the flow rate.

Hyposalivation may be caused due to Iatrogenic reasons while taking certain medications like Antidepressant, Diuretics, Antihypertensives, Antipsychotics, Patients undergoing

Chemotherapy, Radiotherapy to head and neck region and Surgical trauma.

Patients having an Autoimmune disease like Rheumatoid arthritis, Sjogrens syndrome, neurological disorders like mental depression, cerebral palsy, hormonal disorders like Diabetes mellitus, hyper & hypothyroidism, Hereditary disorders like Cystic fibrosis, Ectodermal dysplasia. Certain Metabolic disturbance such as Malnutrition, Dehydration, Vitamin deficiency and local salivary diseases like Sialoliths and Sialadenitis also leads to hyposalivation.[3]

3.4. Salivary Secretory Disorders, Inducing Drugs, and Clinical Management.

4. Xerostomia

Xerostomia may be caused by medication, systemic diseases, pathologies of the salivary glands, and head and neck radiotherapy.[3]

4.1. Drug induced xerostomia

Anticholinergic and antimuscarinic agents are drugs with the capacity to reduce or block the effects produced by acetylcholine on the central and peripheral nervous system. Most anticholinergic agents affect muscarinic gland receptors producing a decrease in salivary secretion. Antidepressants like fluoxetine, with a serotoninergic action have xerostomia as a common side effect. Xerostomia is also seen in patients taking antidepressants (monoamine-oxidase inhibitors, tricyclics, heterocyclics, and others).

Antihypertensive drugs such as the inhibitors of the angiotensin-converting enzyme (captopril and enalapril) may cause the accumulation of bradykinin-tissue mediator which is responsible for a large number of adverse reactions.[3]

4.2. Head and neck radiation

Radiotherapy (RT) of the head and neck region may cause acute side-effects such as mucositis, dysphagia, hoarseness, erythema, and desquamation of the skin and later may appear as chronic injuries to vasculature, salivary glands, mucosa, connective tissue, and bone. Xerostomia is the main complication often seen in irradiated patients as and usually involves a high radiation dose to salivary glands. Radiation-induced xerostomia has an early onset: in the first week, half the patients present a decrease in salivary flow. After 7 weeks of head and neck radiotherapy the salivary flow diminishes up to 20%. Salivary function continues to decline after Radiotherapy and there is minimal long-term recovery.

4.3. Drug-induced sialorrhea and/or drooling

Direct muscarinic agonists like pilocarpine increase cholinergic tone and induce sialorrhea.[3]

5. Management of Xerostomia

Initial treatment of xerostomia is basically palliative, minimizing symptoms and preventing oral complications. The elimination of possible factors for xerostomia such as mouthwashes with an alcoholic content, diet sugar, and toxic habits including alcohol and tobacco.[3]

5.1. Sialogogic drugs

Sialogogic drugs are those agents designed to stimulate salivary secretion and have an effect on the systemic pathway. Therefore,these drugs act upon differing receptor groups that is the Direct and indirect muscarinic agonists,Peripheral adrenergic $\alpha 2$ antagonists and Centrally active agents that diminish adrenergic tone.

Pilocarpine is efficient in Sjogren's Syndrome patients, irradiated and with bone marrow transplants. Pilocarpine dosage is from 5 to 10 mg 1 h before eating, 3 times a day oral route.[4]

Cevimeline Hydrochloride (Evoxac) is used for the treatment of dry mouth syndrome in patients with Sjogren's Syndrome. The recommended dosage is 30 mg 3 times a day.[4]

Bethanechol chloride (Urecholine) is used to decrease unwanted effects caused by antidepressant and antipsychotic drugs and it is administered 4 times a day in doses from 10 to 50 mg.[4]

5.2. Intraoral releasers of saliva substitutes – reservoirs

Certain intraoral devices are designed to deliver a salivary substitute (Oralbalance gel®, K-Y jelly®, Orthana® artificial saliva) for a prolonged period. The patients who are habitually wearing the dental prosthesis can have them built into the prosthetic structure.[3]

5.3. Neuroelectric stimulation

Intraoral electrostimulators with dental splints are used to increase salivary secretion. Other electrostimulation systems like transcutaneous electrical nerve stimulation (TENS) also results in an increase in salivary secretion in healthy patients.[3]

5.4. Sialorrhea and drooling

Patients with sialorrhea may have perioral and/or chin dermatitis, cheilitis and may experience fungal infection. Salivary hypersecretion results in muscular fatigue that is caused by continuous forced swallowing due to excess saliva and it also functionally affect phonation and gustative perception. Atropine helps in reducing drooling when administered sublingually.[3]

In patients with oral candidiasis topical application of miconazole (2%) ointment or gel, Nystatin ointment or oral suspension and systemic treatment with fluconazole, ketaconazole or itraconazole can be used in refractory cases and Immuno-compromised patients.

Symptoms of oral dryness may be alleviated by the use of mouth gels, oral sprays or artificial saliva.

Table 1: ARTIFICIAL SALIVA" contains[3]

Carboxymethyl cellulose	10 gm/L
Sorbitol	30.0 gm/L
Potassium chloride	1.200gm/L
Sodium chloride	0.843gm/L
Magnesium chloride	0.051gm/L
Calcium chloride	0.146gm/L
Dipotassium hydrogen phosphate	0.342gm/L

Hypersalivation : Refers to a measurable increase in function of one or more salivary glands as reflected in the flow rate.[4]

The flow rate and viscosity of saliva would affect the denture construction process and the quality of the final product. A flow of medium viscosity at normal resting salivary flow rate lubricates the mucosa and assists retention of complete dentures.

Patients of denture wearing age take medications that can reduce salivary secretions. Patients who had undergone received radiation therapy in the region of the salivary glands have glandular tissue destruction with resulting reduction in salivary flow.

The palatal glands are destroyed in patients who have worn a complete maxillary denture for many years and is caused due to the pressure atrophy resulting from lost residual alveolar ridge support of the denture.

Excess of saliva complicates the process of denture construction, especially when an impression is made. When new dentures are first inserted, it is common for the patient to experience a temporary increase in salivary flow. The consistency of saliva can range from a thin, serous type to a thick, ropy consistency. It is best to work with a serous type. Thick saliva makes dentures more difficult to wear.

5.4.1. Impression making

1. The amount and consistency of saliva have to be considered while impression making.
2. Drugs (e.g.-atropine sulfate) can be administered orally before making the impression. .
3. The palate is massaged to encourage the glands to empty and the palate is wiped with gauze.
4. Irrigation with an astringent mouthwash is done before inserting the impression material.
5. To milk palatal glands, warm gauze pads are used and to constrict gland opening cold pads are used.

5.4.2. In patients with xerostomia

1. A gentle approach is essential for patients with dry mouth as the mucosa and lips can be traumatized. The lips should be coated with petroleum jelly to help with retraction and access to the oral cavity. The operator's gloved fingers should be wetted to prevent them from sticking to the soft tissues.
2. 'Silicone impression materials' are the best and is least traumatic to the oral mucosa. Zinc oxide eugenol paste causes adhesion and burn the mouth and materials like plaster of paris adhere to the mucosa and results in abrasion.

5.4.3. How to Control of Saliva during Impression for Removable Partial Denture Using Irreversible Hydrocolloid.

1. The alginate is displaced by the excessive amount of thick mucinous saliva, which is secreted by the palatal salivary glands, thus resulting in inaccurate impressions. Saliva can be controlled by having the patient rinse the mouth with an astringent mouthwash and then with cold water.The patient's mouth is packed with a 4x4 inch gauze that has been folded to form an absorptive strip.[5]
2. In the maxillary arch, one gauze strip is extended from the posterior portion of the right buccal vestibule to the posterior portion of the left buccal vestibule. The patient is instructed to hold a second strip against the tissues of the palate.[5]

3. In the mandibular arch, one gauze strip is extended from the right buccal vestibule to the left buccal vestibule. A second gauze strip is positioned in the lingual sulcus by having the patient raise the tongue, placing the gauze, and then having the patient relax the tongue. The gauze should be gently removed immediately before the impression is made.[5]
4. If a mouthwash is not handy, the problem is overcome by employing the " Tandem" impression technique, in which one impression is taken to "soak up" the bubbles and mucinous saliva, followed immediately by a second impression which will record the tissues in are relatively saliva-free state. The use of an antisialagogue, 15mg propantheline bromide tablet taken 30 minutes in combination with mouth rinses and gauze packs may be used to control salivary flow before taking the impression.[5]
5. Antisialagogues should not be prescribed in patients having underlying medical conditions like glaucoma, prostatic hypertrophy, or cardiac conditions in which any increase in heart rate is to be avoided.

5.4.4. How to Control Saliva during Impression for Fixed Partial Denture

1. Saliva can be controlled by using a rubber dam, high-volume vacuum, saliva ejector, svedopter and anti-sialagouges.
2. Drugs used to control flow of saliva include Methantheline bromide (Banthine) and Propantheline bromide (Pro-Banthine).[5]
3. One 50-mg tablet of Banthine or 15-mg tablet of Pro-Banthine taken 1 hour before appointment reduces the salivary flow. Another drug that can be used as an anti-sialagogue is Clonidine hydrochloride.[5]

6. The role of saliva in retention of complete dentures

Saliva is a major factor in evaluating the physical influences that contributes for denture retention.

The physical forces of retention in which saliva involved are:

1. Adhesion
2. Cohesion
3. Interfacial surface tension
4. Capillarity
5. Atmospheric pressure.

7. Adhesion

It is the physical force involved in the attraction between unlike molecules. The limit of the effect of molecular forces is of the order of 10^{-6} per 0.000001 cm. Between the surface of the denture and the mucous membrane of basal seat, there is a layer of saliva which has the thickness of the order of 10^{-2}per 0.01 cm. A layer of saliva between the denture base and the mucosa of the basal seat acts in the same way. The effectiveness of adhesion depends on close adaptation of the denture base to the supporting tissue and is also directly proportional to the area covered by the denture.[6]

8. Cohesion

Cohesion is the physical factor of electromagnetic force acting between molecules of the same material or otherwise called like molecules. Forces of cohesion with water, and approximately with saliva as well, are in the order of 1 Gm. on 1 cm^2, this force is sufficient for overcoming the weight of the denture. Cohesion occurs in the layer of saliva between the denture base and the mucosa and is effective in direct proportion to the area covered by the denture.[6]

9. Interfacial Surface Tension

The phenomenon of surface tension is the force that maintains the surface continuity of a fluid. This results from an imbalance in cohesive forces present at the surface of the layer or column of the fluid. All denture base materials have higher surface tension than oral mucosa, but once coated by salivary pellicle, their surface tension is reduced, which promotes maximizing the surface area between saliva and base. The thin fluid film between the denture base and the mucosa of the basal seat therefore furnishes a retentive force by virtue of the tendency of the saliva to maximize its contact with both surfaces.[6]

10. Capillarity

Capillary attraction or capillarity is a force developed because of surface tension that causes the surface of a liquid to become elevated or depressed when it is in contact with a solid. When the adaptation of the denture base to the mucosa is sufficiently close the space between the denture base and mucosa usually about 0.1mm or less – filled with a thin film of saliva acts as a capillary tube and helps to retain the dentures. The magnitude of the capillary attraction created by the space between the denture base and the mucous membrane is one half in comparison with the example of the attraction in the tubes. The more narrow the space, the greater is the attraction, When good wetting of the walls of the space occurs, the attraction inside the liquid is lowered because of capillary attraction. In the case of the mucous membrane, saliva, and the denture base, the denture is attracted to the mucous membrane by a force whose magnitude responds to the difference of the attraction of the exterior atmosphere and the saliva under the denture. Thus, capillary attraction may be the force which results in denture retention.[6]

11. Atmospheric Pressure

The atmospheric pressure acts as a retentive force when dislodging forces are applied to the denture. Atmospheric pressure itself is supplied by the weight of the atmosphere and amounts to14.7 lb/inch. This means that the retentive force supplied by the atmospheric pressure is directly proportional to the area covered by the denture base. A perfect border seal is essential all around the denture base for this force to be effective. Atmospheric pressure is an emergency retentive force which comes into play when the denture is being pulled away from the basal seat and the negative pressure created between the denture and the basal seat helps in retention.[6]

12. Conclusion

Human saliva is a complex fluid secreted by the major and minor salivary glands and secretion is under the control of the autonomic nervous system. Saliva performs various distinct functions namely cleansing, lubrication, mucosal integrity, buffering, remineralisation, digestion and antimicrobial action.

Research in salivary physiology and chemistry is just a beginning with the recognition of the significance of saliva to oral and dental health. With a more complete knowledge of the profile of normal saliva in health and with ageing, comparison can be made with disease states or prosthetic intervention to determine which aspects of salivary composition are affected.

13. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

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