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Saliva Composition and Functions: A Comprehensive Review

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Abstract

Aim: The aim of this study was to perform a literature review about the composition and functions of saliva as well as describe the factors that influence salivary flow (SF) and its biochemical composition.

Background: Saliva represents an increasingly useful auxiliary means of diagnosis. Sialometry and sialochemistry are used to diagnose systemic illnesses, monitoring general health, and as an indicator of risk for diseases creating a close relation between oral and systemic health.

Review: This review provides fundamental information about the salivary system in terms of normal values for SF and composition and a comprehensive review of the factors that affect this important system.

Conclusion: Since several factors can influence salivary secretion and composition, a strictly standardized collection must be made so the above-mentioned exams are able to reflect the real functioning of the salivary glands and serve as efficient means for monitoring health.

Clinical Significance: Since many oral and systemic conditions manifest themselves as changes in the flow and composition of saliva the dental practitioner is advised to remain up-to-date with the current literature on the subject.

Keywords: Saliva, salivary glands, salivary proteins, lysozyme, lactoferrin

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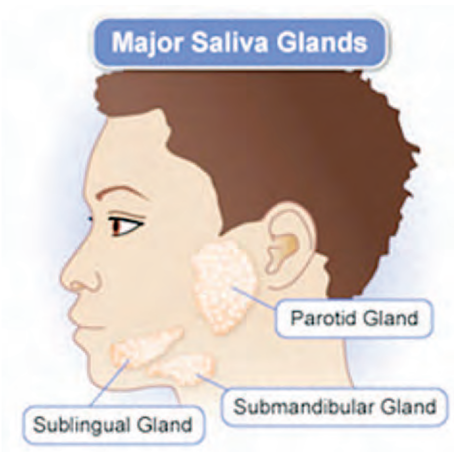
Introduction

Salivary fluid is an exocrine secretion[1,2] consisting of approximately 99% water, containing a variety of electrolytes (sodium, potassium, calcium, chloride, magnesium, bicarbonate, phosphate) and proteins, represented by enzymes, immunoglobulins and other antimicrobial factors, mucosal glycoproteins, traces of albumin and some polypeptides and oligopeptides of importance to oral health. There are also glucose and nitrogenous products, such as urea and ammonia.[3,4] The components interact and are responsible for the various functions attributed to saliva.[2]



Total or whole saliva refers to the complex mixture of fluids from the salivary glands, the gingival fold, oral mucosa transudate, in addition to mucous of the nasal cavity and pharynx, non-adherent oral bacterial, food remainders, desquamated epithelial and blood cells, as well as traces of medications or chemical products.[3-9]

At rest, without exogenous or pharmacological stimulation, there is a small, continuous salivary flow (SF), denominated basal unstimulated secretion, present in the form of a film that covers, moisturizes, and lubricates the oral tissues. Whereas, stimulated saliva is produced in the face of some mechanical, gustatory, olfactory, or pharmacological stimulus, contributing to around 80% to 90% of daily salivary production.[2-4,9-12]

A healthy person's mean daily saliva production ranges from 1 to 1.5L.[4] The SF index is a parameter allowing stimulated and unstimulated saliva flow to be classified as normal, low, or very low (hyposalivation).[8] In adults, normal total stimulated SF ranges from 1 to 3 mL/min, low ranges from 0.7 to 1.0 mL/min, while hyposalivation is characterized by a SF of less than 0.7 mL/min. The normal unstimulated SF ranges from 0.25 to 0.35 mL/min, low ranges from 0.1 to 0.25 mL/min, while hyposalivation is characterized by a SF of less than 0.1 mL/min.[8,11] However, the values denominated "normal" for stimulated and unstimulated SF exhibit a large biological variation. Thus, individual SF must be monitored regularly and not determined as "normal" or "abnormal", based only on one measurement.[9,11]

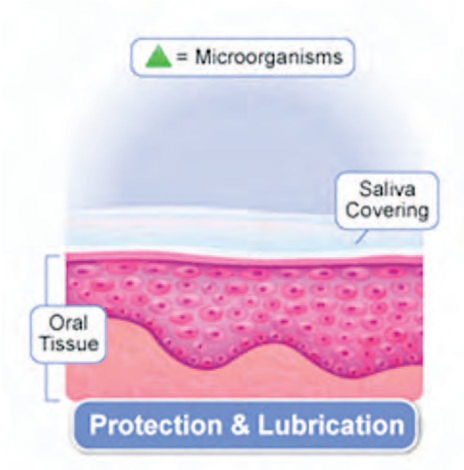
Saliva is critical for preserving and maintaining the health of oral tissues and has been used as a source of non-invasive investigation of metabolism and the elimination of many drugs. However, it receives little attention until its quantity diminishes or its quality becomes altered.[4,7,11,13]

At present, saliva represents an increasingly useful auxiliary means of diagnosis.[14] Many researchers have made use of sialometry and sialochemistry to diagnose systemic illnesses, monitoring general health, and as an indicator of risk for diseases creating a close relation between oral and systemic health.[15] However, since several factors can influence salivary secretion and composition a strictly standardized collection must be made so the above-mentioned exams are able to reflect the real functioning of the salivary glands and serve as an efficient means for monitoring health. Therefore, the aim of this literature review was to investigate the composition and functions of saliva as well as describe the factors that influence SF and its biochemical composition.

Saliva Functions and Composition

Taste

The SF initially formed inside the acini is isotonic with respect to plasma. However, as it runs through the network of ducts, it becomes hypotonic.[6,9,16,17] The hypotonicity of saliva (low levels of glucose, sodium, chloride, and urea) and its capacity to provide the dissolution of substances allows the gustatory buds to perceive different flavors. Gustin, a salivary protein, appears to be necessary for the growth and maturation of these buds.[1,4,13,18]



Protection and Lubrication

Saliva forms a seromucosal covering that lubricates and protects the oral tissues against irritating agents.[18,19] This occurs due to mucins (proteins with high carbohydrate content) responsible for lubrication, protection against dehydration, and maintenance of salivary visco-elasticity. They also selectively modulate the adhesion of microorganisms to the oral tissue surfaces, which contributes to the control of bacterial and fungal colonization. In addition, they protect these tissues against proteolytic attacks by microorganisms. Mastication, speech, and deglutition are aided by the lubricant effects of these proteins.[1,4,8,19-22]

Dilution and Cleaning

Sugars in their free form are present in total stimulated and unstimulated saliva at a mean concentration of 0.5 to 1 mg/100mL.[3,5] High concentrations of sugar in saliva mainly occur after the intake of food and drink.[3,5] It is known there is a correlation between the glucose concentration in the blood and salivary fluid, particularly in diabetics, but because this is not always significant, saliva is not used as a means of monitoring blood sugar.[23]

In addition to diluting substances, its fluid consistency provides mechanical cleansing of the residues present in the mouth such as non-adherent bacteria and cellular and food debris. SF tends to eliminate excess carbohydrates, thus, limiting the availability of sugars to the biofilm microorganisms. The greater the SF, the greater the cleaning and diluting capacity; therefore, if changes in health status cause a reduction in SF, there would be a drastic alteration in the level of oral cleaning.[8,12,13,18,19]

Buffer Capacity

Saliva behaves as a buffer system to protect the mouth[8,19] as follows:

1. It prevents colonization by potentially pathogenic microorganisms by denying them optimization of environmental conditions.
2. Saliva buffers (neutralizes) and cleans the acids produced by acidogenic microorganisms, thus, preventing enamel demineralization.[13]

It is important to emphasize biofilm thickness, and the number of bacteria present determines the efficacy of salivary buffers.[4]

Negatively loaded residues on the salivary proteins work as buffers. Sialin, a salivary peptide, plays an important role in increasing the biofilm pH after exposure to fermentable carbohydrates.[8,13]

Urea is another 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.[3,5,8,9,24,25] Children with chronic renal insufficiency present with less caries than healthy children, due to the increased levels of salivary urea.[26]

Ammonia, a product of urea and aminoacid metabolism, is potentially cytotoxic to gingival tissues. It is an important factor in the initiation of gingivitis because it may increase the permeability of the sulcular epithelium to other toxic or antigenic substances in addition to the formation of dental calculus.[27]

The carbonic acid-bicarbonate system is the most important buffer in stimulated saliva, while in unstimulated saliva it serves as the phosphate buffer system.[8]

Integrity of Tooth Enamel

Saliva plays a fundamental role in maintaining the physical-chemical integrity of tooth enamel by modulating remineralization and demineralization. The main factors controlling the stability of enamel hydroxyapatite are the active concentrations free of calcium, phosphate, and fluoride in solution and the salivary pH.[11,28]

The high concentrations of calcium and phosphate in saliva guarantee ionic exchanges directed towards the tooth surfaces that begin with tooth eruption resulting in post-eruptive maturation. Remineralization of a carious tooth before cavitation occurs is possible, mainly due to the availability of calcium and phosphate ions in saliva.[8,13,18]

The concentration of salivary calcium varies with the SF[8,11] and is not affected by diet. However, diseases such as cystic fibrosis and some medications such as pilocarpine cause an increase in calcium levels. Depending on the pH, salivary calcium can be ionized or linked. Ionized calcium is important for establishing equilibrium between the calcium phosphates of enamel and its adjacent liquid. Non-ionized calcium can be linked to inorganic ions (inorganic phosphate, bicarbonate, fluoride), to small organic ions (citrate), and to macromolecules (statherin, histidine-rich peptides, and proline-rich proteins). A special case of the combination of calcium is its strong link with α-amilase, where it acts as a co-factor necessary for the enzyme function.[8,11]

Inorganic orthophosphate found in saliva consists of phosphoric acid (H_3PO_4) and primary ($H_2PO_4^-$), secondary (HPO_4^{2-}), and tertiary (PO_4^{3-}) inorganic phosphate ions. The concentrations of these ions depend on salivary pH and vary in accordance with the SF. As the flow increases, the total concentration of inorganic phosphate diminishes.[8,11] The most important biological function of this ion is to maintain the dental structure. Another function, discussed previously, is its buffer capacity, relevant only in unstimulated SF.[8,11]

The presence of fluoride in saliva, even at physiologically low levels, is decisive for the stability of dental minerals. Its concentration in total saliva is related to its consumption. It is dependent on the fluoride in the environment, especially in drinking water. Other sources are also important, such as dentifrices and other products used in caries prevention. The presence of fluoride ions in the liquid phase reduces mineral loss during a drop in biofilm pH, as these ions diminish the solubility of dental hydroxyapatite, making it more resistant to demineralization. It has also been demonstrated fluoride reduces the production of acids in biofilm.[4,8,11,28]

Normal salivary pH is from 6 to 7 and varies in accordance with the SF, from 5.3 (low flow) to 7.8 (peak flow). There are various sources of hydrogen ions in oral fluids: secretion by the salivary glands in the form of organic and inorganic acids, production by the oral microbiota, or acquisition through food. These ions influence the equilibrium of calcium phosphates in the enamel. The higher the concentration of hydrogen ions, the lower the pH and vice versa.[4,8] At higher flows of stimulated salivary secretion, the concentration of bicarbonate ions is higher, the pH also rises, and the buffering power of the saliva increases dramatically.[11]

Digestion

Saliva is responsible for the initial digestion of starch, favoring the formation of the food bolus.[13,17] This action occurs mainly by the presence of the digestive enzyme α-amylase (ptyalin) in the composition of the saliva. Its biological function is to divide the starch into maltose, maltotriose, and dextrins. This enzyme is considered to be a good indicator of properly functioning salivary glands,[29] contributing 40% to 50% of the total salivary protein produced by the glands. The greater part of this enzyme (80%) is synthesized in the parotids and the remainder in the submandibular glands. Its action is inactivated in the acid portions of the gastrointestinal tract and is consequently limited to the mouth.[3,4,8,12,21]

Tissue Repair

A tissue repair function is attributed to saliva since clinically the bleeding time of oral tissues appears to be shorter than other tissues. When saliva is experimentally mixed with blood, the coagulation time can be greatly accelerated (although the resulting clot is less solid than normal). Experimental studies in mice have shown wound contraction is significantly increased in the presence of saliva due to the epidermal growth factor it contains which is produced by the submandibular glands.[13]

Antibacterial Properties and Participation in Film and Calculus Formation

Saliva contains a spectrum of immunologic and non-immunologic proteins with antibacterial properties. In addition, some proteins are necessary for inhibiting the spontaneous precipitation of calcium and phosphate ions in the salivary glands and in their secretions. Both the acquired film and the biofilm have proteins derived from saliva.[3,11]

Secretory immunoglobulin A (IgA) is the largest immunologic component of saliva. It 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.[4,11,13,21] Other immunologic components, such as IgG and IgM, occur in less quantity and probably originate from gingival fluid.[3,4]

Among the non-immunologic salivary protein components, there are enzymes (lysozyme, lactoferrin, and peroxidase), mucin glycoproteins, agglutinins, histatins, proline-rich proteins, statherins, and cystatins.[11,21]

Lysozyme can hydrolyze the cellular wall of some bacteria, and because it is strongly cationic, it can activate the bacterial “autolisines” which are able to destroy bacterial cell wall components. Gram-negative bacteria are more resistant to this enzyme due to the protective function of their external lipopolysaccharide layer. Other antibacterial mechanisms have been proposed for this enzyme, such as aggregation and inhibition of bacterial adherence.[3,4,8,21,22]

Lactoferrin links 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 also provides fungicidal, antiviral, anti-inflammatory, and immunomodulatory functions.[3,4,8,22,30]

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. As a result of its consumption, proteins and cells are protected from the toxic and oxidant effects of hydrogen peroxide.[3,4,8,22]

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. They favor oral structure lubrication, and it is probable both are important in the formation of acquired film. Another function proposed for the proline-rich proteins is the capacity to selectively mediate bacterial adhesion to tooth surfaces.[3,4,8,22]

The cystatins are also related to acquired film formation and to hydroxyapatite crystal equilibrium. Due to its proteinase inhibiting properties, it is surmised they act in controlling proteolytic activity.[3,4,8,22,31]

The histatins, a family of histidine-rich peptides,[22] have antimicrobial activity against some strains of *Streptococcus mutans*[32] and inhibit hemoagglutination of the periopathogen *Porphyromonas gingivallis*.[33] They neutralize the lipopolysaccharides of the external membranes of Gram-negative bacteria[34] and are potent inhibitors of *Candida albicans* growth and development.[35] The bactericidal and fungicidal effects occur through the union of positively loaded histatins with the biological membranes resulting in the destruction of their architecture and altering their permeability. Other functions attributed to these peptides are: participation in acquired film formation and inhibition of histamine release by the mastocytes, suggesting a role in oral inflammation.[21]

Salivary agglutinin, a highly glycosylated protein frequently associated with other salivary proteins and with secretory IgA, is one of the main salivary components responsible for bacteria agglutination.[22]

Factors Influencing Salivary Flow and Composition

Several factors may influence SF and its composition. As a result, these vary greatly among individuals and in the same individual under different circumstances.[3,5,9,10,36]

Individual Hydration

The degree of individual hydration is the most important factor that interferes in salivary secretion.[10] When the body water content is reduced by 8%, SF virtually diminishes to zero, whereas hyperhydration causes an increase in SF.[9] During dehydration, the salivary glands cease secretion to conserve water.[37]

Body Posture, Lighting, and Smoking

SF varies in accordance with body posture, lighting conditions, and smoking. Patients kept standing up or lying down present higher and lower SF, respectively, than seated patients. There is a decrease of 30% to 40% in SF of people that are blindfolded or in the dark. However, the flow is not less in blind people, when compared with people with normal vision. This suggests that blind people adapt to the lack of light that enters through the eyes. Olfactive stimulation and smoking cause a temporary increase in unstimulated SF.[9] Men that smoke present significantly higher stimulated SF than non-smoking men.[38] The irritating effect of tobacco increases glandular excretion,[39] and nicotine causes severe morphologic and functional alterations in the salivary glands.[40]

The Circadian and Circannual Cycle

SF attains its peak at the end of the afternoon but goes down to almost zero during sleep. Salivary composition is not constant and is related to the Circadian cycle.[4,41] The concentration of total proteins attains its peak at the end of the afternoon, while the peak production levels of sodium and chloride occur at the beginning of the morning.[9]

According to Edgar,[9] the circannual rhythm also influences salivary secretion. In the summer lower volumes of salivary flows from the parotid gland, while in the winter there are peak volumes of secretion. However, these data were obtained in the state of Texas in the southern United States and the reduction in SF may be associated with dehydration that occurs because of the hot weather.

Medications

Many classes of drugs, particularly those that have anticholinergic action (antidepressants, anxiolytics, antipsychotics, antihistaminics, and antihypertensives), may cause reduction in SF and alter its composition.[9,18,42,43]

Thinking of Food and Visual Stimulation

Thinking of food or looking at food are weak salivation stimuli in humans. It may seem that people salivate simply because of thinking of food, but in reality they become more conscious of the saliva in the floor of the mouth between swallows. Some researchers observed a small increase in SF in the face of visual stimuli, while others observed no effect whatever.[9]

Regular Stimulation of Salivary Flow

Although there is evidence regular stimulation of SF with the use of chewing gum leads to an increase in stimulated SF, further studies are required to explain whether this stimulation increases unstimulated SF.[9]

Size of Salivary Glands and Body Weight

Stimulated SF is directly related to the size of the salivary gland, contrary to unstimulated SF which does not depend on its size.[9]

Unstimulated SF appears to be independent of body weight;[10] on the other hand, obese boys present significantly lower salivary amylase concentration in comparison with controls.[44]

Salivary Flow Index

The main factor affecting salivary composition is the flow index[8,9] which varies in accordance with the type, intensity, and duration of the stimulus.[5,12,17] As the SF increases, the concentrations of total protein, sodium, calcium, chloride, and bicarbonate as well as the pH increases to various levels, whereas the concentrations of inorganic phosphate and magnesium diminish.[3,8]

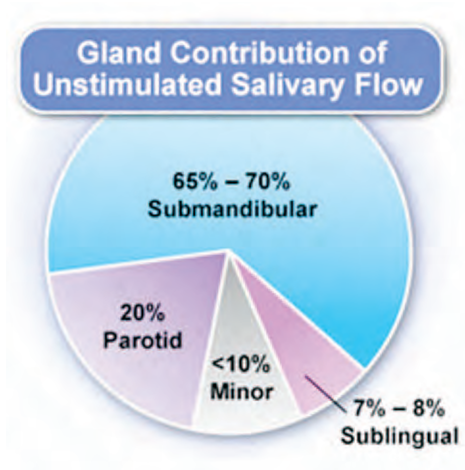
Mechanical or chemical stimulus is associated with increased salivary secretion. The action of chewing something tasteless itself stimulates salivation but to a lesser degree than the tasty stimulation caused by citric acid.[9] Acid substances are considered potent gustatory stimuli.[10]

Contributions of Different Salivary Glands

Other factors that influence total salivary composition are the relative contribution of the different salivary glands and the type of secretion.[5,9] The percentage of contribution by the glands during unstimulated SF is as follows:

- 20% by the parotid glands
- 65%-70% submandibular glands
- 7% to 8% sublingual glands
- <10% by the minor salivary glands

When SF is stimulated, there is an alteration in the percentage of contribution of each gland with



the parotids contributing over 50% of the total salivary secretion.[3,4,11,12,45]

The salivary secretions may be serous, mucous, or mixed. Serous secretions, produced mainly by the parotids, are rich in ions and enzymes. Mucous secretions are rich in mucins (glycoproteins) and present little or no enzymatic activity. They are produced mainly by the smaller glands. In the mixed glands, such as the submandibular and sublingual glands, the salivary content depends on the proportion between the serous and mucous cells.[2,8,13,17]

Physical Exercise

Physical exercise can alter secretion and induces changes in various salivary components, such as: immunoglobulins, hormones, lactate, proteins, and electrolytes.[46,47] In addition to the determined intensity of the exercise, there is a clear rise in salivary levels of α-amilase and electrolytes (especially Na^+).[46] During physical activities sympathetic stimulation appears to be strong enough to diminish or inhibit salivary secretion.[47]

Alcohol

The intake of a single high dose of ethanol causes a significant reduction of stimulated SF. This diminishment results from the altered release of total proteins and amylase as well as in diminished release of electrolytes.[29] Rats exposed to ethanol for a prolonged period showed significant reduction in salivary secretion and diminished release of proteins.[40]

Systemic Diseases and Nutrition

In some chronic diseases such as: pancreatitis, diabetes mellitus, renal insufficiency, anorexia, bulimia, and celiac disease, the amylase level is high.[2] Alterations in the psycho-emotional state may alter the biochemical composition of saliva. Depression is accompanied by diminished salivary proteins.[48] Nutritional deficiencies may also influence salivary function and composition.[4,11]

Fasting and Nausea

Although short-term fasting reduces SF it does not lead to hyposalivation, and the flow is restored to normal values immediately after the fasting period ends.[11] Stimulated SF increases when preceded by gustatory stimulation in less than one hour before saliva collection.[49] Saliva secretion increases before and during vomiting.[9]

Age

Despite numerous studies on salivary secretion the effect of aging on SF remains obscure due to conflicting observations in the literature leaving little information available regarding SF in healthy elderly persons.[50]

Histologic analyses have demonstrated with advancing age the parenchyma of the salivary glands is gradually replaced by adipose and fibrovascular tissue, and the volume of the acini is reduced.[51,52] However, functional studies among healthy individuals indicate aging itself does not necessarily lead to diminished glandular capacity to produce saliva.[19]

Navazesh et al.[53] found the total unstimulated SF is significantly lower in healthy patients between the ages of 65 and 83 years, in comparison with patients between the ages of 18 and 35 years. However, total stimulated SF was significantly higher in the elderly in comparison with the younger persons.

Percival et al.[50] also found the total unstimulated SF is related to age, being significantly reduced in healthy non-medicated elderly persons aged 80 years or older. However, no age-related reductions in stimulated SF from the parotid were detected. It is suggested the elderly do not present dysfunctions in the ability to respond to sialogogues, however, the reduction in unstimulated SF could contribute to the appearance of diseases in the oral mucosa.

Lima et al.[54] demonstrated elderly persons presented a very low daily saliva production, and this appears to be more related to systemic diseases and the continuous use of medications than to aging.

Gender

The differences in salivary secretion between men and women have been attributed to two theories: women present smaller salivary glands in comparison with men and the female hormonal pattern may contribute to diminished salivary secretion.[50] However, menopause and hormone replacement therapy are not associated with salivary dysfunction of the parotid.[55] There were no significant differences with regard to SF between healthy pre- and post-menopausal women and between post-menopausal women under hormonal treatment and women that did not receive treatment.[56]

Percival et al.[50] found healthy, non-medicated women presented a lower mean for total unstimulated SF and for stimulated SF of the parotid when compared with men. Whereas, Shern et al.[57] reported the total unstimulated SF was not influenced by gender.

Conclusion

Since several factors can influence salivary secretion and composition a precise standard for saliva collection must be established. Such a standard would make the test results obtained through sialometry and/or sialochemistry more helpful in characterizing the true functional state of the salivary glands which in turn would serve as indicators for a diagnosis when oral and/or systemic alterations are suspected.

Clinical Significance

Since many oral and systemic conditions manifest themselves as changes in the flow and composition of saliva the dental practitioner is advised to remain up-to-date with the current literature on the subject.

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