Review Article

# Human saliva and its role in oral and systemic health

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**ABSTRACT**

Saliva is a unique fluid and interest in it as a diagnostic medium has advanced exponentially in the past 10 years. Advances in the use of saliva as a diagnostic fluid have been tremendously affected by current technological developments. As a consequence, these advances in technology have helped to move saliva beyond measuring oral health characteristics to where it now may be used to measure essential features of overall health. This review paper sums up various researches that have been conducted on human saliva and its composition with physiological aspects. It mainly highlights the composition, physiology, and role of saliva as a diagnostic fluid in oral and systemic health.


**KEY WORDS:** Diagnostic fluid, Oral health, Proteins, Saliva

## INTRODUCTION

The saliva - a clinically informative biological fluid, has gained a lot of interest due to its physiologic diagnostic medium.[1] Its major components include a broad spectrum of proteins and peptides, nucleic acids, electrolytes, and hormones.[2] The major salivary gland contributes to secrete 93% of the saliva, whereas the remaining 7% is secreted by minor salivary glands. The salivary composition contains 99% water and 1% solvent molecules (organic and inorganic) with a paramount value of quantity as well as quality.[3] The salivary glands are composed of acinar and ductal cells. A large serous secretion is produced by the acinar cells of the parotid glands. The production of calcium by acinar gland is lesser as compared to submandibular gland; however, it does synthesize most of the alpha-amylase. The submandibular glands are responsible for producing mucins along with the sublingual glands. It also produces proline and histatin-rich proteins in conjunction with the parotid.[4] Daily secretion rates range between 500 and 700 ml and the average volume in the mouth is 1.1 ml. Saliva production is controlled by the autonomous nervous system. At rest, secretion ranges from 0.25 to 0.35 ml/min and is mostly produced by the submandibular and sublingual glands. Sensory, electrical, or mechanical stimuli can raise the secretion rate to 1.5 ml/min. The greatest volume of saliva is produced before, during, and after meals, reaching its maximum peak at around 12 a.m., and falls considerably at night, while sleeping.[5]


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## CLINICAL IMPORTANCE OF THE QUANTITY AND QUALITY OF SALIVA IN MAINTAINING ORAL HEALTH

While the quantity of saliva is important, so is its quality, as each of its components performs a series of specific functions (Summarized in Table 1).[6]

## PHYSIOLOGY OF SALIVA

The three major salivary glands are parotid, submandibular, and sublingual glands, 800–1000 minor salivary glands are present throughout

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**Table 1: Saliva components and functions**[6]

| Functions | Components |
|---|---|
| Lubrication | Mucin, proline-rich glycoproteins, water |
| Antimicrobial action | Lysozyme, lactoferrin, lactoperoxides, mucins, cystins, histatins, immunoglobulins, proline-rich glycoproteins, IgA |
| Maintaining mucosa integrity | Mucins, electrolytes, water |
| Cleansing | Water |
| Buffer capacity and remineralization | Bicarbonate, phosphate, calcium, statherin, proline-rich anionic proteins, fluoride |
| Growth factor components | EGF, FGF, and NGF. Mode of action: Binding with high-affinity EGF on the cell surface and stimulates the intrinsic protein tyrosine kinase activity of the receptor |
| Inflammatory mediators | Interleukin and tumor necrosis factor enhance the action of chemical carcinogens, due to which mutated cells and further accumulation of genetic damage get proliferated |
| Preparing food for swallowing | Water, mucins |
| Digestion | Amylase, lipase, ribonucleases, proteases, water, mucins |
| Taste | Water, gustin |
| Phonation | Water, mucin |
| Antimicrobial, antiviral, antifungal, and antibacterial | Modification of bacteria's metabolism and its ability to adhere to the tooth surface comes under this function. The overgrowth of oral microbial populations by bacterial lysis is prevented by the lysozyme enzyme. The components involved are mucins, immunoglobulins, cystatins, human defensins, histatins, lactoferrin, agglutinin, lysozyme, and lactoperoxidase |

EGF: Epidermal growth factor, FGF: Fibroblast growth factor, NGF: Nerve growth factor

the oral submucosa. Approximately 600 ml of serous and mucinous saliva, which includes 99% water and 1% other important compounds such as minerals, electrolytes, buffers, and enzymes, are produced by the human salivary glands each day.[7] Each type of gland is responsible for producing a special type of secretion. The parotid glands produce serous fluids, the submandibular glands produce seromucous secretion, and the sublingual glands secrete mucous saliva. Secretions from individual salivary glands are also evaluated for detecting gland-specific diseases such as infection and obstruction. However, the whole saliva is most frequently studied when the salivary analysis is used for the evaluation of systemic disorders. A collection of saliva can take place with as well as without stimulation.[8] Stimulated saliva is collected by masticatory action (i.e., from a subject chewing on paraffin) or by gustatory stimulation (i.e., application of citric acid on the subject's tongue). Unstimulated saliva is collected without exogenous gustatory, masticatory, or mechanical stimulation. The whole saliva can be collected by the draining method, in which saliva is allowed to drip off the lower lip, and the splitting method, in which the subjects expectorate saliva into a test tube.[9]

## TRANSFER OF BIOMOLECULES FROM BLOOD TO SALIVA

Ultrafiltration through the tight junctions between the cells of secretary units is the most common route. Ultrafiltration also occurs through the spaces between the acinus and ductal cells. The molecules must be relatively small to follow this type of system.[10] A serum molecule reaching saliva by diffusion must cross five stages: The capillary wall, the interstitial space, the basal cell membrane of the acinus cell or duct cell, and the cytoplasm of the acinus or duct cell, and the luminal cell membrane. The molecule's size and the electric charge it carries are partly the decisive factors of the ability of a molecule to diffuse passively through cell membranes. It will be difficult for a polar molecule or a charged ion in a solution to pass through the phospholipid membrane.[11]

## MAIN CAUSES OF HYPO- AND HYPER-SALIVATION

A number of physiological circumstances reduce salivary secretion. They include age, the number of teeth in the mouth, male/female, body weight, and the time of day. In relation to age, although submaxillary and sublingual gland secretion may be slightly diminished in older persons, the same cannot be said of the parotid glands, and a reduction in the unstimulated total saliva but good response to stimulation may be observed despite the presence of other factors such as polymedication or certain disorders such as diabetes, dehydration, and hypertension which may aggravate the clinical symptoms.[12] Other pathological conditions also affect salivary flow. Over 400 medicines, many of them in common use, induce salivary gland hypofunction. Table 2 shows the drug groups that have been most directly linked to salivary hyposecretion.[13] Head and neck radiotherapy causes irreversible hyposalivation by destroying the glandular parenchyma. The adverse effects start from 4000 rads onward and the reduction in salivary flow depends on the dose. Some systemic disorders cause progressive destruction of the salivary glands, as in some autoimmune diseases such as Sjögren's syndrome,[14] while others lead to vascular

**Table 2: Medicines and drugs with side effects on salivary secretion[13]**

| Medicine group | Examples |
|---|---|
| Anorectic | Fenfluramine |
| Anxiolytics | Lorazepam, diazepam |
| Anticonvulsants | Gabapentin |
| Antidepressants | Tricyclic amitriptyline, imipramine |
| Antidepressants | SSRI sertraline, fluoxetine |
| Antiemetics | Meclizine |
| Antihistaminics | Loratadine |
| Antiparkinsonian | Biperiden, selegiline |
| Antipsychotics | Clozapine, chlorpromazine |
| Bronchodilators | Ipratropium, albuterol |
| Decongestants | Pseudoephedrine |
| Diuretics | Spironolactone, furosemide |
| Muscle relaxants | Baclofen |
| Narcotic analgesics | Meperidine, morphine |
| Sedatives | Flurazepam |
| Antihypertensive | Prazosin hydrochloride antiarthritic |

or neurological alterations that have transitory and reversible repercussions on saliva production, as in hypertension, depression, malnutrition, dehydration, diabetes, etc.

Physiologically, the greatest salivary secretion takes place during tooth eruption and is linked to hyperstimulation of the peripheral receptors in the oral mucus. Hyperstimulation of salivary secretion also takes place during the first half of pregnancy and menstruation, as well as resulting from smell and mechanical stimuli such as mastication and taste stimuli such as sourness and sweetness. The pathological causes of hypersalivation include those of oral origin such as the first stages of wearing dentures, dental pain or any irritation, or inflammatory process in the oral-pharyngeal or digestive regions, particularly in the upper tract. Certain neurological disorders such as Parkinson's disease, epilepsy, encephalitis, or some tumors can cause hypersalivation, as can exogenous poisoning by lead, bismuth, mercury, silver, gold, or arsenic and endointoxications such as uremia, and certain medicines such as pilocarpine, cholinesterase inhibitors, cholinergic agonists, lithium, iodides, mercury compounds or L-dopa, hyperparathyroidism, and some stages of serious infectious processes; it is also associated with Riley-Day syndrome.[15]

## DIAGNOSTIC ROLE OF SALIVA

Several pathways both intra- and extra-cellular enable the saliva to be reached by some substances that are not among its normal components. The most common intracellular pathways are passive diffusion and active transport. Ultrafiltration through the tight cell junctions is the best-known extracellular mechanism. Some molecules may enter the saliva from the serum by passing through the capillary barrier, the interstitial spaces, and the membranes of the acinar and ductal cells until they reach the excretory tubules. Serum components may also reach the saliva through the crevicular fluid. This raises the prospect of using saliva in the diagnosis of certain pathologies.[16]

1. Advantages of Saliva as a diagnostic tool
   As the saliva can be collected by a non-invasive method, it has been proved to be beneficent to avoid the complications associated with needle infections. This method has been proved to be valuable for the elderly patients who have a decreased blood count or subjects with physical or mental challenges.[17] This prevents the cross-contamination, which could eventually occur due to improperly collected blood specimens. For steroid hormone evaluation, saliva depicts an active level free hormone concentration rather than the bound form as observed with the serum level. Therefore, saliva serves as a more efficient fluid for the steroid hormone monitoring for measuring the menopausal fluctuations, whereas steroids in the blood are bound to the globulin molecules.[18]

2. Cardiovascular diseases
   Cardiovascular disease is a major cause of death worldwide. Markers in saliva may be useful in post-operative follow-up among patients undergoing cardiovascular surgery. The biomarkers in saliva such as C-reactive proteins, myoglobin, brain natriuretic peptide (NT-proBNP), and cardiac troponin (cTnl) may be helpful for post-operative cardiovascular patients.[19] This includes the total salivary amylase; the estimation of salivary amylase is being evaluated for every 6 h after the surgery. Decreased salivary amylase level has been found for the patient with a ruptured aortic aneurysm. The salivary amylase provides a direct and end point for catecholamine activity for the patients with altered heart rate in a stressed condition.[20]

3. Endocrine function
   The plasma steroid levels are monitored for the clinical assessment of endocrine function, the steroid hormone in plasma shows the active level of these hormones. At present, the saliva is being more commonly used to evaluate the steroid hormone levels. These include the cortisol, dehydroepiandrosterone, estradiol, estriol, testosterone, and progesterone.[21] This may be helpful to evaluate the cognitive-emotional behavior and predict the individual's sexual activity. In addition, the ovarian function and the risk of preterm birth can be further evaluated by assaying the salivary steroid levels.

4. Infectious diseases (viral and bacterial)
   The potential use of salivary estimation is beneficial to evaluate human immunodeficiency virus (HIV). The enzyme-linked fluorescence technique combined with western blot assays has been used for saliva testing to determine the sensitivity and

specificity. The efficacy of saliva as a diagnostic tool has alleviated its association along with the traditional diagnostic methodology. HIV-infected patient can now be screened for HIV-1 and HIV-2 with the help of salivary-based enzyme-linked immunosorbent assay accompanied by a western blot for further confirmation.[22] In addition, a significant progress has been observed with the identification of various other infections which includes viral hepatitis, dengue, Zika virus, and malaria.[23]

5. The technological discovery of salivary biomarkers
   The diagnostic role of saliva is still facing the technological barriers due to the presence of complex constituents with lower quantity. However, with the emergence of advanced technology during the past decade, the analyses of proteins and nucleic acids have provided a broader horizon to overcome these challenges. The current research on salivary proteins has shown that though a lower concentration of proteins is present in saliva, these proteins can still play an important role in the diagnosis of various acute and chronic diseases. The principle analysis of salivary proteomes briefs the complex spectrum of oral and general health consequences and unveils the disease progression at an early stage. The protein expression is generally analyzed by polyacrylamide gel electrophoresis (PAGE).[24] PAGE discriminates between the similar types of different complex compounds, these even provide help to identify different isoforms of the same polypeptide. The mass spectrometry introduces more specific separation along with PAGE, these constituents can further be categorized using Electrospray Ionization and matrix-assisted laser desorption ionization.[25]

6. Barriers and challenges associated with salivary collection
   As the salivary specimens are collected by direct spitting into the tube or the method of absorption by cotton balls, these specimens are non-sterile and serve as a medium for bacterial progression. However, many different companies patented their saliva collection devices such as Oasis Diagnostics, DNA Genotek, and Salimetrics.[26] Other barriers are clinician and insurance companies have to accept this test as authenticate so the investment can be promising for the development of the standardization of sampling.

7. Autoimmune disorders
   Sjogren's syndrome is a chronic, autoimmune disorder characterized by salivary and lacrimal gland dysfunction, serologic abnormalities, and multiple organ system changes. Attempts have been made to use saliva for the conclusive diagnosis of Sjogren's syndrome.[3] With the exception of sialometry (salivary flow rate determination), most salivary function tests must be conducted in special laboratories or clinics. These tests include sialography, salivary scintigraphy, biopsies, and serological tests. While these tests are helpful, they are invasive, expensive, and not always conclusive proposed a panel of salivary determinants that could be used clinically for the diagnosis of Sjogren's syndrome. These include flow rate, pH, buffer capacity, *Lactobacillus*, and yeast concentration. Other investigators have measured specific cytokine concentrations in the saliva in Sjogren's syndrome patients for their possible diagnostic utility. The results of these studies suggest that salivary IL-2 and IL-6 concentrations are significantly elevated among individuals suffering from Sjogren's syndrome.[3]

8. Psychiatry
   Saliva may also be useful in providing objective outcome measures during psychiatric therapy. For example, saliva has been used to monitor therapeutic responses in the treatment of anxiety by measuring salivary levels of 3-methoxy-4-hydroxyphenylglycol. Saliva also has been used to measure post-traumatic stress disorder associated with wartime.[27] It would seem that potential applications of salivary monitoring in psychiatry are worthy of further exploration.

## CONCLUSIONS

The molecular diagnostics of saliva have proved a valuable early stage detection of various infectious and systemic diseases. Saliva, as biological fluid, is rich in diagnostic biomarkers for both the oral and systemic disorders. The interest in saliva as a diagnostic tool is due to the fact that the collection of the sample is easy and simple with non-invasive interventions, therefore, avoiding the risk of infection spread.

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