Review Article

# Saliva and Salivary Diagnostics: A review

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## Abstract

Saliva is a complex fluid which is secreted by the salivary glands. While the quantity of saliva is important, so is its quality, as each of its components performs a series of specific functions. Adequate salivary flow and composition are recognized as important for lubrication and protection of soft and hard oral tissues. Protection of soft tissues is provided against desiccation, penetration, ulceration, and potential carcinogens by mucin and anti-proteases. This is achieved through clearance, aggregation, and reduced adherence by both immunological and non-immunological means as well as direct antimicrobial activity. Saliva is effective in maintaining pH in the oral cavity by its buffer capacity and contributes to the regulation of dental biofilm pH and enamel surface integrity. The wide spectrum of molecules present in saliva provides valuable information for clinical diagnostic applications. The advantage of salivary diagnostics is that it offers an easy, inexpensive, painless, and stress free approach to disease detection. Hence, in this paper, we aim to review the components of saliva, its functions in maintaining oral health, and the main factors that cause alterations in saliva secretion and its role as a potential diagnostic tool.

**Keywords:** Saliva, Diagnostic tool, Oral health, Salivary biomarkers.

## Introduction

The equilibrium of the oral cavity is maintained by the saliva, an exocrine fluid mostly produced by the major salivary glands (parotid, submandibular, and sublingual) secreted in the mouth through small apertures called salivary ducts.[1] It is sterile when it leaves the salivary glands, but ceases to be so as soon as it mixes with the crevicular fluid, which remains of food, microorganisms, desquamated oral mucous cells, etc.[2]

The major salivary glands are the main contributors of saliva. The parotid gland produces a largely serous secretion, while the mucins are mainly produced by the submandibular and sublingual glands. The minor salivary glands are essentially mucous except for von Ebner's gland which is purely serous in nature. On an average around, 500 and 700 ml of saliva are produced daily. Saliva secretion is controlled by the autonomous nervous system with the volume produced varying according to the type and intensity of stimulation. A greater volume is produced before, during, and after meals, whereas a lower salivary production is observed during sleep.[3]

The wide spectrum of molecules present in saliva provides valuable information for clinical diagnostic applications. Whole saliva is most frequently used for diagnosis of systemic diseases, because it can be easily collected and it contains most of the serum constituents.[4] Hence, in this paper, we aim to review the components of saliva, its functions in maintaining oral health, and the main factors that cause alterations in saliva secretion and its role as a potential diagnostic tool.

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## Components of Saliva

Saliva consists of 99% water, 1% protein, and electrolytic salts, including sodium, potassium, calcium, magnesium, bicarbonate, and phosphates. Immunoglobulins, proteins, enzymes, mucins, and nitrogenous compounds including urea and ammonia are also found in saliva. When these compounds are mixed, saliva performs a variety of functions.[5]

## Functions of Saliva

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

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**Table 1: Functions of Saliva**

| Function | Effect | Active constituent |
|---|---|---|
| Protection | Lubrication | Glycoprotein |
| | Waterproofing | Water |
| | Lavage | |
| | Pellicle formation | |
| Buffering | Maintains pH unsuitable for colonization | Phosphate and bicarbonate |
| | Neutralizes acid | |
| Digestion | Bolus formation | Water |
| | Neutralizes esophageal contents | Phosphate and bicarbonate |
| Taste | Solution of molecules | Gustin |
| | Taste bud growth and maturation | |
| Antimicrobial action | Barrier | Glycoprotein |
| | Antibodies | Ig A |
| | | Lysozyme |
| | | Lactoferrin |
| Tooth integrity | Enamel maturation | Calcium and phosphate |
| | Repair | |

**Table 2: Summary of various salivary biomarkers in malignancies[22]**

| Salivary biomarker | Site of Cancer |
|---|---|
| lncRNA | Oral squamous cell carcinoma |
| CCNI, EGFR, FGF19, FRS2, and GREB1 | Lung cancer |
| P53 | Oral squamous cell carcinoma |
| AGPAT1, B2M, BASP2, IER3, and IL1B | Ovarian cancer |
| CA15-3 | Breast cancer |
| c-erb-2 | Breast cancer |
| CA 125 | Oral, breast, and ovarian cancer |
| FGF2 | Salivary gland tumors |
| PSA | Prostate adenocarcinoma |
| lactate dehydrogenase | Oral squamous cell carcinoma |
| Salivary adenosine deaminase (ADA) | Carcinoma of tongue |

PSA: Prostate specific antigen, FGF2: Fibroblast growth factor 2

## Role of Saliva in Maintaining Oral Health

Decreased production of saliva is known as hyposalivation or hypoptyalism and significantly affects the individual's quality of life as well as his or her oral health. The main symptoms and signs associated with hyposalivation are a 'dry mouth' feeling or xerostomia, difficulty in swallowing, speaking, eating dry foods and in wearing dentures, the need to drink water frequently, pain and irritation of the mucosa, a burning feeling in the tongue, and dysgeusia. The signs most frequently encountered are loss of glossiness of the oral mucosa, dryness of the mucosa, which become thin and cracked, fissures in the dorsum of the tongue, angular cheilitis, thick saliva, increased frequency of oral infection, especially by *Candida* spp., presence of caries in atypical locations, and increased size of major salivary glands.[7]

Less frequently, salivary secretion can increase. This is called hypersalivation, ptyalism, or sialorrhea and it may be physiological or pathological. It is diagnosed in patients who complain of the need to constantly having to swallow saliva or in patients with cerebral palsy or other severe neurological disorders.[8]

Both hypo- and hypersalivation have physiological and pathological causes. Decreased salivary flow is caused by certain drugs, radiotherapy, and some systemic diseases. The pathological causes of hypersalivation include 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, exogenous poisoning by lead, bismuth, mercury, silver, gold or arsenic and endointoxications such as uremia, and certain medicines such as pilocarpin, cholinesterase inhibitors, cholinergic agonists, lithium, iodides, mercury compounds or L-dopa, and hyperparathyroidism can also lead to hypersalivation.[9]

## Role of Saliva in Diagnosis

The wide spectrum of molecules present in saliva provides valuable information for clinical diagnostic applications. Whole saliva is most frequently used for diagnosis of systemic diseases, because it can be easily collected and it contains most of the serum constituents. Salivary diagnostics can be used for the following diseases/conditions.

## Autoimmune Diseases

Sjogren's syndrome: It is a chronic autoimmune disease characterized by salivary and lacrimal dysfunction, multiple organ abnormalities, and serological changes. Salivary secretions from these patients exhibit elevated levels of antibodies and cytokines such as IgA, IgG, prostaglandin-E2, and interleukin-6. This is accompanied by a reduction in oral phosphate levels and xerostomia due to reduced salivary flow, which can lead to infections, progressive caries, dysphagia, and oral pain.[10]

## Cardiovascular Diseases

Acute coronary syndromes refer to a group of clinical syndromes which include ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina. It is characterized by atherosclerotic plaques which rupture and cause clinical symptoms ranging from chest pain to acute myocardial infarction (AMI). Salivary markers of cardiovascular diseases include C-reactive protein), myoglobin (MYO), creatinine kinase myocardial band, cardiac troponins, and myeloperoxidase, which, when used in combination with an ECG, show a positive correlation with myocardial infarct patients as compared to healthy controls. The salivary MYO levels are significantly higher within 48 h of onset of chest pain in AMI patients.[11] Increased levels of salivary lysozyme

have been shown to be associated with hypertension, an early stage of cardiovascular disorders.[12]

## Genetic Disorders

Cystic fibrosis a hereditary disease which is considered an exocrinopathy characterized by an alteration in electrolyte transport in the epithelial cells and the secretion of viscous mucus by the glands and epithelia is linked to raised sodium, chloride, calcium, phosphate, lipid, and protein contents in the submaxillary saliva. An epidermal growth factor with low biological activity compared to that of healthy persons and raised prostaglandin E2 levels is also found in the saliva of these patients.[13]

Ectodermal Dysplasia the most common form of ectodermal dysplasia is the X-linked hypohidrotic ectodermal dysplasia (HED). Lexner *et al*. performed a study on whole saliva flow and composition in males affected by HED and the female carriers. He found that there was reduced whole saliva flow and the concentration of inorganic constituents and total protein was high. However, the activity and the concentration of the alpha-amylase in the saliva were reduced.[14]

## Dental Caries and Periodontal Diseases

Saliva also has its use in monitoring the level of oral bacteria in it. The increased numbers of *Streptococcus mutans* and lactobacilli in saliva have been associated with increased caries prevalence and root caries.[4] Periodontal diseases have been associated with increased levels of aspartate aminotransferase (AST) and alkaline phosphatase. Salivary AST can be used as a marker for monitoring periodontal disease. Lower levels of uric acid and albumin in the saliva were associated with periodontitis and diabetes. This could be attributed to the oxidative stress present in the oral cavity during these conditions.[15]

## Diseases of the Adrenal Cortex

The hyperfunction of the gland leads to primary hyperaldosteronism, Cushing's syndrome, and adrenogenital syndrome, whereas hypofunction causes Addison's disease and selective hypoaldosteronism. Measurement of elevated late-night salivary cortisol usually at 2300–2400 h is a very reliable tool to the diagnosis of Cushing's syndrome.[16]

## Drug Level Monitoring

Saliva has gained importance for its use for drug monitoring and detection of illicit drugs. Saliva is used to detect the presence of nicotine, cannabinoids, cocaine, phencyclidine, opioids, barbiturates, diazepines, amphetamines, and ethanol. In drug level monitoring, only the unbound fraction of the drug in serum diffuses into the saliva and is detectable in the saliva. The most important diagnostic application of saliva is in the evaluation of illicit drug use. The drug appears in the saliva during the same duration as the serum, and thus, its mere presence is satisfactory for forensic purposes.[17]

## Infections

Diagnosis of bacterial and viral pathogens in the saliva is based on combination assay that measures both antibody and antigen or antibody and nucleic acid. Bacterial Infections – *Mycobacterium tuberculosis* can be detected in saliva by PCR during the acute phase of the disease when the bacterial load is high.[4] *Helicobacter pylori* is found in patients with chronic gastritis and gastric ulcers. It binds to salivary mucins MUC-5B and MUC 7 secreted by the mucous and serous acinar cells of the seromucous salivary glands, respectively. Higher levels of salivary MUC-5B and MUC7 could be used as an indicator for infection with *H. pylori*.[18]

*Viral Infections* – Both viruses and bacteria can be identified by a single target. The oral sample which is obtained by swabbing the buccal mucosa and tongue contains a mixture of sIgA, IgG, IgM, and a rich source of antibodies.[4] Salivary IgM can be used for the detection of measles.[19]

The diagnosis of HIV (human immunodeficiency virus) which causes AIDS is done with Western blot test. The sample is obtained via blood or saliva. p24 antigens and antibodies can be detected against both HIV-1 and HIV-2. Apart from this, salivary proteins can be detected which play a role in immunosurveillance.[20]

## Renal Diseases

The various salivary markers associated with end stage renal disease include nitrite, pH, sodium, chloride, uric acid, cortisol, alpha-amylase, and lactoferrin. Salivary phosphate has been widely used as a clinical biomarker for hyperphosphatemia and studies have shown that salivary phosphate may serve as a superior marker than serum phosphate levels for diagnosis of heart disease and chronic renal failure.[21]

## Malignancy

Early detection is the key to good prognosis in almost all types of cancer. Saliva has been used as a diagnostic medium for oral squamous cell carcinoma, and salivary analytes such as proteins, mRNA, and DNA have been used in their diagnosis (Table 2).[22]

## Forensics

Salivary analysis has been widely used for forensics as salivary samples can be easily obtained from glasses, cigarettes, food products, envelopes, and other sources. A wide majority of patients secrete blood group antigens into their saliva which can be used for the identification of crime suspects and for paternity law suits. Identification of DNA in saliva by genetic profiling can be helpful in cases of sexual abuse and harassment.[23]

## Conclusion

Saliva a complex fluid plays a critical role in the oral environment. It serves as a promising option for diagnosing

certain disorders and monitoring the evolution of certain pathologies or the dosage of medicines or drugs. Salivary metabolomics is a new advancement in the field of salivary diagnostics which analyzes a large array of low molecular weight endogenous metabolites present in the saliva for the detection of diseases The greatest milestone in salivary diagnostics is to identify the disease biomarkers and to transfer it from the laboratory to the clinical practice. However, the growth of salivary diagnostics has been hindered due to lack of sensitive detection methods, lack of correlation between the biomolecules in the blood and saliva, and the circadian variations in saliva. However, unlike blood and other body fluids, salivary diagnostics offers an easy, inexpensive, painless, and stress free approach to disease detection.

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