Review article

Saliva: Composition, Functioning and its Diagnostic Implications – A Review

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ABSTRACT

Saliva is considered to be as a profound biological fluid that is a collection of lot of components and they have their own features. It contributes in good oral health and helps in maintaining and assisting the oral environment. In addition, there are many advantages to employing saliva as a substrate for diagnostic analysis as its component levels are severely affected in case of oral and systemic diseases such as xerostomia, salivary gland disorders, diabetes, autoimmune diseases, radiotherapy, chemotherapy etc. Also, the ease of the sample collection provides the distinctive advantages such as the patient compliance, non-invasiveness, easy storage, repeated collection etc. Several advances have been introduced in the past years for the sensitive detection and quantification of a varied biomarkers that are identified in saliva reflecting the human system, using different methods including Mass Spectrometry (MS), Reverse Transcription-Polymerase Chain Reaction (RTPCR), microarrays, Enzyme Linked Immuno-Assay (ELISA) etc. In future researches, gap is subsequently closing between the use of salivary fluids and the other biofluids in the diagnostic applications. The salivary samples are found to be much reliable in diagnosis when compared to serum sample. This article recollects the overview about the multipurpose body fluid in relation to its clinical significance.

Key-words: Saliva, Diagnostic, Oral Health, Biomarkers

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Introduction

Saliva is an aqueous fluid found in the oral cavity composed of various organic and inorganic components which is released from the major and minor salivary glands. The major salivary glands comprise three paired glands: the parotid (serous), the submandibular (mixed) and the sublingual glands (mixed). The parotid glands are found behind the ramus of the mandible, anterior to the ear. Their secretions reach the oral cavity via stensen's duct. The submandibular glands lie under the body of the mandible. Wharton's duct runs from each gland across the floor of mouth and opens under the anterior part of the tongue. The sublingual glands (the smallest major gland) are found underneath the anterior tongue Some sections of these glands open into Wharton's duct; the remainder secrete via a number of small ducts (Bartholin's ducts) which lie beneath the tongue. The minor salivary glands are distributed throughout the oral cavity in the buccal and labial mucosa, the posterior palate, and the labial border of the tongue.[1,2] Saliva is most important and versatile biological fluid of the body which reflects the oral and systemic health in many ways. Saliva plays a major role in the oesophageal physiology, digestive process, gastric cell protection etc. It also takes mucosal protection, gustatory sensitivity,

lubrication etc.[3]. Each component of salivary fluid performs its specific function and shadows the normal state & internal characteristics of an individual. It also plays a major role in the diagnostic & clinical areas as the analysis of saliva is considered to be as a non-invasive and cost-effective method for the sample collection.

The effectiveness of the saliva for the evaluation of physiological and pathological conditions has been proven in many ways as the functions, composition, interaction with the other systems is readily altered in diseased state. Biomarkers present in saliva are objective, quantifiable components of biological processes. According to the National Institute of Health (NIH), "a biomarker is a characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathogenic process or pharmaceutical response to therapeutic intervention".[4] Additionally, the simplicity of the fluid collection & its diagnostic variation has raised the advances to use it as an alternative or indicator applicable for basic and clinical purposes especially in dentistry and other medical areas as well. At time, the boundless literature is available expressing the efficacy of saliva in health and diseases and describing the role of each and every component in visualising the characteristics in terms of healthy state of an individual.

The possible use of saliva as a specimen for diagnosis is due to its exchange with the substances that compose the plasmatic liquid. This occurs due to the presence of a thin layer epithelial cells separating the salivary ducts from the systemic circulations, making it possible for substances to be transferred into the saliva through active carriage, diffusion through the membrane (ultrafiltration) or through possible diffusion via concentration gradient.[5] The current knowledge on salivary composition, functions, provides the synopsis for the clinical implications.

Composition of Saliva

Whole saliva is most frequently studied when salivary analysis is used for the evaluation of systemic disorders. Saliva is a complex secretion and is comprised of 99% water. The rest 1% is composed of the organic and the inorganic substances. About 93% by volume is secreted by the major salivary glands and the remaining 7% by the minor glands. The normal pH of saliva is 6 to 7 with a range from 5.3 to 7.8. Table 1[6] , shows the different components of saliva with the varying range in mg/100ml.

Functions of Salivary Components and their Clinical Significance

1.Salivary Alpha Amylase (SAA)- Amylase is the single most abundant protein in saliva. It is generally thought to be involved in the initial digestion of starch-containing foods. However, this seems unlikely because its activity is greatly reduced as soon as it reaches the acidic environment of the stomach. Pancreatic amylase is much more likely to be involved in starch digestion.[7] So why then is there so much amylase in saliva? It may be more important in the post-mastication clearance of food from the mouth. Although best known as an enzyme specific to maltose conversion to glucose, amylase is very efficient at converting many non-soluble complex polysaccharides into smaller soluble units. This has two advantages: the dissolution of food particles stuck on teeth and the reduction of the availability of substrates for microbial growth and it displays inhibitory activity against micro-organisms, plays a major role in modulation of bacterial adhesion and growth on intraoral surfaces.[8] An amylase may be considered as an inflammatory biomarker in periodontal disease. SAA is produced locally in the oral cavity by salivary gland in response to β adrenergic stimulation by the process of exocytosis.[9]

2.Mucins - Mucins also perform an antibacterial function by selectively modulating the adhesion of microorganisms to oral tissue surfaces, which contributes to the control of bacterial and fungal colonization. Secretions from the sublingual and submandibular glands contain a high-molecular-weight, highly glycosylated mucin (MG1) and a low-molecular-weight, single-glycosylated peptide chain mucin (MG2). An important part of the multifunctional role of salivary mucins in preserving mucosal integrity is their ability to regulate intercellular calcium levels.[10,11] Salivary mucins provide a protective coating on the hard and soft tissues of the mouth. The selective deposition of salivary mucin on the tooth surface appears to play a central role in the formation of the acquired enamel pellicle.

3.Interleukins - The immune system is the barrier against infectious microorganisms that affect the oral cavity.[12] The complex network of cytokines that intervene in the immune response of the host against external attacks include pro-inflammatory cytokines, anti-inflammatory cytokines and receptor cells for these cytokines.[13]

Interleukins are cytokines which play an important role in communication between inflammatory cells following the activation of the immune system.[14] It would, therefore, be of great interest to know which of them act as mediators in various oral inflammation. The most commonly studied interleukin is IL-1β and most authors agree that it is higher in the saliva and/or crevicular fluid of patients with gingivitis. Therefore, it could be used as a diagnostic marker of the degree of inflammation in gingivitis and can further be studies for other diseases. Moreover, as far as

the other interleukins studied are concerned, there is no clear consensus among the authors.[15]

4.Immunoglobulins - Immunoglobulins (Igs) are protein molecules produced by special cells in organisms' immune systems in response to the presence of the penetration of external agents, such as viruses, bacteria, protozoans, fungi, tumor cells, or tissues that are recognized as foreign because of the presence of cell surface antigens. Igs are also present in saliva, where they act to provide protection of the oral cavity. In particular, IgA, which are produced by the plasma cells of the salivary glands, are the most represented Ig type in salivary fluid and, together with the action carried out by the subgingival microflora, exert a protective action against the oral bacteria.[16,17]

Secretory IgA System (SIgA) is the principal immunoglobulin isotype found in saliva and all other secretions. It exists as a polymeric molecule composed of two (or more) IgA monomers (300,000 Da) and a secretory component (SC) (70,000 Da). It has been observed that cigarette smoking can alter the salivary system by increasing salivary fluid, reducing certain salivary enzymes (i.e., amylase, lactic dehydrogenase, and acid phosphatase), and altering anti-oxidizing enzymes (i.e., glutathione peroxidase) and immune system function.[18,19] Hence, a reduction of the Igs contained in saliva can

represent an increased risk factor for the host

mucosa with respect to pathogenic microorganisms, including periodontal pathogens.[20]

5.Glucose - Saliva is said to be the ultrafiltrate of blood. Glucose is one of the blood components that are transferable across the salivary gland epithelium in proportion to its concentration in blood. Whole saliva is the biologic fluid that is simple to collect.[21] If a glucose level measuring procedure is developed that can monitor glucose level noninvasively, it will make early detection of DM possible. Normal glucose levels in saliva are 0.5–1.00 mg/100 ml and do not considerably have an effect on oral health or support the growth of microorganisms. Biochemistry reveals that the normal value of salivary glucose in a healthy nondiabetic individual is <2 mg/dl.

6.Inorganic Components - The highest and abundant component in saliva is water (approximately 99%), followed by ions $H_2PO_4^-$, F^-, Na^+, Cl^- Ca^{2+}, K^+, HCO_3^-, I^-, Mg^{2+}, thiocyanate. The ionic composition of saliva is different from the plasma that derived from it.[22] The hypotonicity hydrates various organic compounds that form a protective coating on the oral mucosa and facilitates taste sensitivity. Resultant bicarbonate act as a buffering agent, also calcium and phosphate neutralize acids that would otherwise inhibit tooth mineral integrity.[22,23]

Sodium is one of the important electrolytes among all the electrolytes present in the oral cavity that includes chlorine, calcium, potassium and bicarbonate. It played certain role that is important to maintain a normal body function. Sodium helps to control blood pressure, and regulates the function of muscles and nerves, which is why sodium concentration are carefully controlled by the body.[24] The adequate Intake of sodium is 1.2 to 1.5 grams per day.[25]

Chlorine is another important electrolyte present in the saliva. It is a major mineral nutrient that occurs primarily in body fluids. Chloride is a prominent negatively charged ion of the blood, where it represents 70% of the body's total negative ion content. On average

an adult human body contains approximately 115 grams of chloride, making up about 0.15% of total body weight.[26] The overview of

functions of saliva is given is Figure 1.[27]

Diagnostic Efficacy of Saliva in Oral and Systemic Health

Most commonly used laboratory diagnostic procedures involve the analyses of the cellular and chemical constituents of blood. Saliva offers some distinctive advantages when used for diagnosis of diseases. Whole saliva can be collected non-invasively, and by individuals with limited training, including the patient.[28] Tumour tissue and body fluid such as saliva or blood (serum and plasma) can potentially carry whole cells as well as protein, DNA, and RNA species that allow for detection of cellular alterations related to cancer. Compared to the tissue biopsy, body fluids have garnered much more attention for biomarker identification [29]. Examples of using body fluids for tumor detection include sputum for lung cancer diagnosis,[29] urine for urologic tumors, saliva for OSCC, breast fluid, as well as serum or plasma for almost all types of cancer.[30] Considering the accuracy, efficacy, ease of use and cost effectiveness, salivary diagnostic tests have demonstrated their applications in clinical and basic sciences. Moreover, salivary-based diagnostic techniques can potentially allow screening of an entire population for a specific disease in a timely fashion. It has been suggestive as a chair-side diagnosis for multiple oral and systemic diseases at the dental office.[31] Despite the regular screenings and check-ups, many diseases are undetected until a late phase where morbid symptoms become apparent. To overcome these challenges, researchers are unravelling biomarkers. Biomarkers help us to understand the relationship between exposure to various environmental chemicals, development of diseases and identification of groups that are at increased risk for disease.[32]

Considering the complexity of the body fluids, saliva has the advantages of easily accessible in a non-invasive manner, low background of normal material (cells, DNR, RNA, and proteins) and inhibitory substances and less complex than blood. The fallen cells in oral cavity allow saliva to be the first choice of screening and the identification for the potential biomarkers in the pathological conditions like OSCC, which is also helpful in monitoring its development. These biomarkers include genetic material (eg. DNA, RNA) and protein molecules that reflect the current physiological state of an individual and hence help scientists to better understand the underlying cause of a disease.[33] Due to its ease and non-invasive accessibility along with its abundance of biomarkers such as genetic material and proteins,[33] saliva has been studied extensively as a potential diagnostic tool over the last decade.[34]

Various studies have shown the presence of salivary biomarkers in several common oral and systemic diseases. Varied types of inflammatory biomarkers associated with both oral diseases, as well as systemic diseases are reported such as interleukins-1β, -6 and -8 (IL-1β, -6 and -8), tumour necrosis factor-α (TNF-α) and matrix metalloproteinases (MMP)-8 and -9.[35,36,37,38,39] An increasing number of specific molecular markers for different diseases, such as oral and breast cancer, cardiovascular diseases and human immunodeficiency virus (HIV) are being identified.[40,41,42] In case of cancer, both serum and salivary levels are seen elevated predominantly for the Interleukins. In the previous studies, oral infections, hyperglycaemia, hypertension and metabolic syndrome show a significant association with increased salivary levels of lysozymes.

Advantages of salivary testing for diagnosis include : Non-invasive, easy to use, cost effectiveness, safer to administer than serum sampling (no needles), real-time diagnostic values, no need for trained medical staff, multiple samples can be obtained easily, collection and screening can be done at home, minimal risks of cross-contamination, more economical sampling, shipping and storage is easy compared to serum, requires less manipulation during diagnostic procedures compared to serum, commercial availability of screening assays.[43,44,45] Various systemic diseases alter the salivary functions following the clinical manifestations affecting the salivary glands. The examples of few diseases leading to the qualitative changes in the salivary composition are given in Table 2.[46] Although blood will remain the gold standard for diagnosis of diseases and drugs, but saliva collection offers an alternative to serum as a biological fluid to be useful in diagnostic applications.

Conclusion

Saliva is a versatile body fluid predicting higher importance in physiological and pathological

Whole (mixed)	Resting		Stimulated	
	Mean	**Range**	**Mean**	**Range**
Total solids	500	300–800	530	400–900
Organic Constituents				
Proteins	220	140–640	280	170–420
Amino acids			4	
Amylase	38			
Lysozyme	22		11	0.4-62
IgA	19			
IgG	1.4			
Glucose	0.2			
Citrate	1.0		1.0	0.5-3
Lactate			Trace	
Ammonia			3	1-12
Urea	20	12–70	13	0.6–30
Uric acid	1.5	0.5–3	3	1–21
Creatinine	0.1	0.05–0.2		
Cholesterol	8	2.5–50		
CAMP	7		50	
Inorganic constituents				
Sodium	15	0–20	60	
Potassium	80	60–100	80	
Thiocyanate-smoker	9	6–12		
Thiocyanate -Non-smokers	2	1–3		
Calcium	5.8	2.2–11.3	6	
Phosphate (P)	16.8	6.1–71	12	
Chloride	50		100	
Fluoride (ppm)	0.028	0.015–0.045		

Table 1: Composition of Saliva

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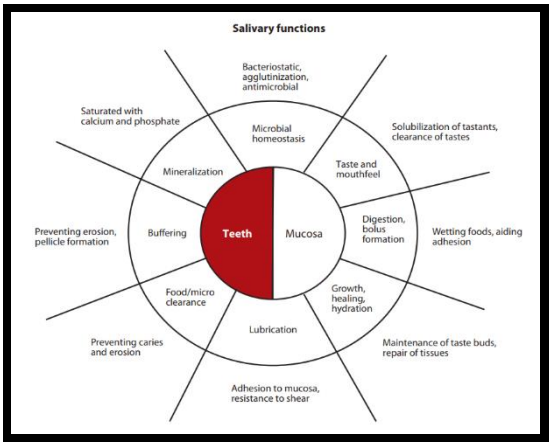

Figure 1: The functions of saliva can be divided according to the surface, i.e., the teeth or mucosa. Some functions, such as lubrication and microbial homeostasis, are common to both surfaces, whereas most other functions are unique to the surface. Some proteins have been assigned to different functions, but the list is not definitive and is based on available research.[27]

Systemic Diseases affecting Salivary Glands and Saliva
1. Sjogren's Syndrome, Rheumatoid diseases, myasthenia gravis
2. Cancer
3. Cirrhosis
4. Cystic fibrosis
5. HIV Infection
6. Hypertension
7. Hormonal disorders
8. Malnutrition, dehydration, vitamin deficiency
9. Renal diseases
10. Sarcoidoisis
11. Parkinsonism, Alzheimer's disease

Table 2: Representing the systemic diseases affecting the salivary glands and production of saliva.

situations of human body. The composition and functions of saliva and its secretion is complex; however, the salivary components/biomarkers are widely contributing in the laboratory investigations such as infectious diseases diagnosis, malignancies, chronic systemic diseases, eliciting drug abuse etc. The generous advantages of using saliva when compared to plasma samples are that it is easy to collect, non-invasive, simple to handle, low-cost storage etc. Though the levels of biomarkers are lower in saliva as compared to plasma but the non-invasive collection offers an alternative to be useful in diagnostic applications. Future researches should subsequently focus on the development of better technology for the sensitive detection and specific quantification of salivary biomarkers.

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Conflict of Interest

There is no Conflict of interest

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