REIVEW ARTICLE

Human Saliva and Its Role in Oral & Systemic Health

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ABSTRACT:

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 how biomolecules came to saliva via a blood and role of saliva as a diagnostic fluid in oral and systemic health. Over 33,000 published papers were found electronically when search keywords – such as humans, diagnosis, salivary, etc. were used. We have been very specific in including recent research papers for the literature search and aim to provide a comprehensive overview ofthe current status of human saliva and its importance as a diagnostic fluid in disease detection such as cardiovascular diseases (CVD), endocrine and contiguous diseases. A number of psychological and pathological factors contribute towards variations in salivary flow. This paper further illustrates major factors, which cause alterations in salivary secretion and the importance of saliva along with its role as a diagnostic agent for certain pathologies.

KEYWORDS: saliva; diagnostic fluid; proteins; and oral health.

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INTRODUCTION

The Saliva – a clinically informative biological fluid, has gained a lot of interest because of 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 the minor 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].In Table **1**, detailed discussion on how composition of saliva helps in different function for the maintenance of oral health.[2]

The daily secretion rate of minor salivary gland essentially secretes mucous up to 500ml to 700ml whereas, the average volume in the mouth is 1.1 ml/per minute. The saliva production is controlled by the nervous system and the secretion ranges from 0.25 ml/min to 0.35 ml/min at the

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basal metabolic rate. Certain sensory, electrical, or mechanical stimulation can raise the secretion rate to 1.5ml/min.[6]

Table 1. Description of human saliva function and composition help in performing functions [5].

Function	Composition
Lubrication	The lubrication of hard and soft oral surfaces has been provided with help of mucin, proline-rich proteins, and water.
Buffering action	Regulation of pH in the oral cavity by combinations of bicarbonate ions, phosphate ions, and proteins aids in buffering action.
Lavage/ Cleansing	The presence of water in saliva helps to remove the debris and micro-organisms in order to maintain and preserve oral hygiene.
Mucosal integrity	Prevention of bacterial adhesion to the tooth enamel takes place by the presence of mucins, electrolytes, and water.
Remineralisation	Remineralisation takes place by the help of supersaturated saliva. The components involved in this function are calcium, phosphate, statherin, and anionic proline-rich proteins.
Taste and digestion of carbohydrates	Water, gustins, amylase, lipase, protease, mucins, and ribonuclease helps for the breakdown and digestion of carbohydrates, fats, and proteins.
Growth factor	*Components:* epidermal growth factor (EGF), fibroblast growth factor (FGF), and nerve growth factor (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 tumour necrosis factor enhances the action of chemical carcinogens, due to which mutated cells and further accumulation of genetic damage get proliferated.
Anti-microbial, anti-viral, anti-fungal, and anti-bacterial	Modification of bacteria's metabolism and its ability to adhere to the tooth surface comes under this function. The over-growth 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 lacto peroxidase.

The fact that the highest volume of saliva is produced around meals has been proved by various research studies. The maximum peak is reached at around 12 a.m., with a significant fall while sleeping.[7] The salivary function includes maintaining the integrity of oral structures in personal relationships, digestion of food, and regulating the cause of oral infections.[7] Saliva also plays a major role in protecting the teeth from caries.[8] These can be subdivided into four categories: (i) diluting and eliminating sugars and other substances (ii) buffer capacity (iii) balancing demineralisation and (iv) anti-microbial action.

1. Physiology of Saliva

The three major salivary glands are Parotid, submandibular, and sublingual glands, 800 to 1000 minor salivary glands are present throughout the oral submucosa. Approximately 600 ml of serous and mucinous saliva, which includes 99% water and 1% other important compounds like minerals, electrolytes, buffers and enzymes, are produced by the human salivary glands each day.[9] Each type of gland is responsible for producing a special type of secretion. The parotid glands produce serous fluids, the submandibular glands produce sero-mucous 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.[10] 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 expectorates saliva into a test tube.[11]

2. 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 in order to follow this type of system.[12] A serum molecule reaching saliva by diffusion must cross 5 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. In addition, molecules are transported into saliva through transudation of plasma compounds into the oral cavity. This could be from gingival crevicular fluid or directly by the oral route.[13]

THE DIAGNOSTIC ROLE OF SALIVA

It has been analysed that human saliva can be obtained by various non-invasive techniques and can demonstrate various biomarkers for the detection and monitoring of body diseases.[14] Therefore, there is an increased interest of investigators to screen, diagnose and monitor the normal functioning of the human body using saliva. The screening of steroid and peptide hormones, antibodies and the therapeutic drug abuse can be monitored via salivary functions. The steroid hormone analysis can be measured at home by multiple specimens; this may be helpful in measuring the reproductive cycles, stress anxiety and menopausal variations. The drug abuse can be monitored without using any blood drawing procedures.[15,16] The onset of infectious diseases can be monitored via measuring the antibody level in human body.[17] Therefore, saliva has been observed as a diagnostic tool for various diseases. Saliva, besides serving as an effective and inexpensive diagnostic fluid has also served as a rapid medium for evaluation of various analytes.[18]A number of studies have been conducted which have analysed multiple scenarios associated with the blood and saliva as a diagnostic tool.[8,16,19]Some of them have favoured the salivary diagnosis whereas; some of them formulated difficult setups.

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.[20] 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.[21]Due to the diurnal variations in the reproductive cycle, steroid hormones are needed to be collected late night or early morning, or daily at the same time of day to observe the variations in the cycle. These multiple specimens when collected via blood serves too expensive for the patient.

2. Saliva provides potential diagnostics

The methodology for saliva assay has been improving with time due to the ease in its collection. The human salivary proteins serve diagnostic value for several systemic diseases,

2.1. Cardiovascular disease

The cardiovascular disease is being the major cause of mortality worldwide. The biomarkers in saliva such as; C-reactive proteins, myoglobin, brain natriuretic peptide (NT-proBNP) and cardiac troponin (cTnl) may be helpful for postoperative cardiovascular patients.[22] This includes the total salivaryamylase; the estimation of salivary amylase is being evaluated for every six hours after the surgery. Decreased salivary amylase level has been found for the patient with a ruptured aortic aneurysm. The salivary a-amylase provides a direct and end point for catecholamine activity for the patients with altered heart rate in a stressed condition.[23,24]

2.2. 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. Currently, the saliva is being more commonly used to evaluate the steroid hormone levels. These include the cortisol, dehydroepiandrosterone, estradiol, estriol, testosterone and progesterone. [21,25]This may be helpful to evaluate the cognitive-emotional behaviour and to predict the individual's sexual activity. Additionally, the ovarian function and the risk of preterm birth can be further evaluated by assaying the salivary steroid levels.

2.3. 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 help of salivary-based enzyme enzyme-linked immunosorbent assay (ELISA) accompanied by a western blot for further confirmation.[26] Additionally, a significant progress has been observed with the identification of various other infections which includes viral Hepatitis, Dengue, Zika virus and Malaria.[27–29]

3. 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 last decade, the analyses of proteins and nucleic acids have provided a broader horizon to overcome these challenges.[30] The current research on salivary proteins has shown that albeit a lower concentration of proteins are present in saliva, but these proteins can still play an important role in thediagnosis 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 anearly stage. The protein expression is generally analysed by PAGE (polyacrylamide gel electrophoresis).[31,32] PAGE discriminates between the similar types 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 by using electro spray ionization (ESI) and matrix-assisted laser desorption ionization (MALDI).[33]

4. 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 amedium for bacterial progression. However, many different companies patented theirsaliva collection devices such as Oasis diagnostics, DNA Genotek, and Salimetrics. [34,35]Other barriers are clinician and insurance companies have to accept this test as authenticate so the investment can be promising for the development ofstandardisation of sampling.

CONCLUSIONS

The molecular diagnostics of saliva have proved a valuable early stage detection of various infectious and systemic disease. 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 thesample is easy and simple with non-invasive interventions, therefore, avoiding the risk of infection spread. A new technology known as Point of Care (PoC) technology will soon be available in dental practices that can be utilizedfor an early screening or detection of various systematic diseases on spot. However, further studies are warranted in this area.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

ZK and **JH:** bring this idea and start compiling papers from different database such as Pubmed and scopus.

RSK and **MA:** help in write up and designing of tables. **MSZ** and **SN:** did their expert help for the improvement and final proof read.

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