review

J. Stomat. Occ. Med. (2015) 8:83–86
DOI 10.1007/s12548-015-0133-7

international journal of
stomatology &
occlusion medicine

Diagnostic efficacy of saliva in oral and systemic health

Tanya Khaitan · Arpita Kabiraj · Preeti Tomar Bhattacharya · Uday Ginjupally · Harshvardhan Jha

Received: 12 April 2015 / Accepted: 31 July 2015 / Published online: 5 October 2015

Abstract Saliva has the potential to become a first-line diagnostic sample of choice owing to the advancements in detection technologies coupled with combinations of biomolecules with clinical relevance. Saliva is increasingly being used as an investigational aid in the diagnosis of oral and systemic diseases. It is a complex fluid containing a variety of enzymes, hormones, antibodies, antimicrobial constituents, and growth factors. Thus, saliva is functionally equivalent to serum, but its low concentration compared with serum levels in the blood may prevent salivary diagnostics from being clinically practical. However, with the development of new and highly sensitive techniques the low concentration of analytes in saliva is no longer a limitation. Evaluation of the secretions from individual salivary glands is useful for the detection of gland-specific pathology and whole saliva is used for the evaluation of systemic disorders. This review article highlights the diagnostic applications of saliva for systemic diseases and for monitoring of general health.

Keywords Diagnosis · Biomarkers · Sjögren's syndrome · Malignancy · Saliva

T. Khaitan (✉)
Department of Oral Medicine and Radiology, Haldia Institute of Dental Sciences and Research,
Haldia, West Bengal, India
e-mail: tanyakhaitan@gmail.com

A. Kabiraj
Department of Oral Pathology and Microbiology, Haldia Institute of Dental Sciences and Research,
Haldia, West Bengal, India
e-mail: drarpita4u@yahoo.com

P. T. Bhattacharya
Department of Oral Medicine and Radiology, Haldia Institute of Dental Sciences and Research,
Haldia, West Bengal, India
e-mail: preeti_kgmu@rediffmail.com

U. Ginjupally
Department of Oral Medicine and Radiology, Kamineni Institute of Dental Sciences,
Narketpally, Andhra Pradesh, India
e-mail: uday2361@gmail.com

H. Jha
Haldia Institute of Dental Sciences and Research,
Haldia, West Bengal, India
e-mail: harshvardhan.spartan@gmail.com

Introduction

Saliva has been well documented as a mirror of the body's health because it contains the serum constituents that are measured in standard blood tests to monitor health and diseases. Although saliva is an inimitable fluid and diagnostic medium, its use as an analytical fluid has been hindered, mainly because of our poor understanding of the biomolecules present in it and their significance in disease etiology, combined with the lack of high-sensitivity detection systems [1].

Saliva harbors a wide spectrum of proteins/peptides, nucleic acids, electrolytes, and hormones that originate from multiple local and systemic sources. It is sterile when it leaves the salivary glands but ceases to be so as soon as it enters the oral cavity and comes into contact with food remains, microorganisms, desquamated oral mucous cells, etc. About 99 % of saliva is water and the other 1 % is a complex of organic and inorganic molecules [2].

There are two types of saliva: gland-specific and whole saliva. Gland-specific saliva can be collected directly from major salivary glands (i.e., parotid, submandibular, and sublingual glands) and approximately 600 minor glands in the oral cavity. Evaluation of the secretions from individual salivary glands is predominantly useful for the detection of gland-specific pathology whereas

whole saliva is useful for the evaluation of systemic disorders [3]. This review article highlights the diagnostic applications of saliva for systemic diseases and for the monitoring of general health after an extensive search of the PubMed/Medline and EBSCO databases within the last 15 years.

Diagnostic applications

Some systemic diseases affect salivary glands directly or indirectly, and may influence the quantity as well as the composition of saliva. These distinctive changes may append to the diagnosis and early detection of such diseases. Saliva can be analyzed for the diagnosis of the following conditions: hereditary disease, autoimmune disease, malignancy, and infections. It can also be used for the monitoring of levels of hormones and drugs, bone turnover markers in saliva, forensic evidence, dental caries and periodontal disease, oral disease with relevance for systemic diseases and occupational and environmental medicine [3–5].

The aforementioned systemic and local diseases are considered in this review because they are more predominant conditions affecting the population worldwide. Saliva is preferred to blood and other body fluids owing to better patient compliance and its less invasive procedure, its easy availability, and its cost effectiveness. Moreover, with the emergence of novel and highly sensitive procedures (e.g., molecular diagnostics, nanotechnology), the low concentration of analytes in saliva is no longer a constraint.

Hereditary diseases

Cystic fibrosis is a genetically transmitted disease of children and young adults predominantly affecting the exocrine glands. Increased levels of sodium chloride concentration and insoluble calcium–protein complexes in sweat, chronic obstructive pulmonary disease, and pancreatic insufficiency have been observed in patients with cystic fibrosis. Hypohidrotic ectodermal dysplasia (HED) is also an X-linked disorder associated with salivary hypofunction [6]. Lexner et al. [7] found reduced whole saliva flow and increased concentration of inorganic constituents and total protein in male patients affected by HED and in female carriers [7]. A strong correlation has been found between 17-hydroxyprogesterone levels in saliva and serum in patients with 21-hydroxylase deficiency. In patients with celiac disease, IgA and antigliadin antibody detection in saliva has high specificity and low sensitivity, whereas determination of these antibodies in serum is highly sensitive and less specific [4, 5].

Autoimmune diseases

Sjögren's syndrome is a chronic autoimmune disorder characterized by salivary and lacrimal gland dysfunction, serologic abnormalities, and multiple organ system changes. Sialography, salivary scintigraphy, and sialochemistry are significant diagnostic tests beside biopsy of the minor salivary glands of the lip for Sjögren's syndrome. An unswerving finding is the increased concentration of sodium, chloride, IgA, IgG, lactoferrin, β2-microglobulin, lysozyme C, cystatin C, cystatin S, albumin, α2-microglobulin, lipid and inflammatory mediators such as prostaglandin E_2, and thromboxane B_2 in the saliva of Sjögren's disease patients [4, 6]. Salivary cytokines interleukin (IL)-2 and IL-6 are increased while levels of amylase, carbonic anhydrase, and phosphate are decreased in these patients. Any alterations in Ss anti-La antibodies can also be used as an indicator of Sjögren's syndrome as well as in the follow-up of its progression. Since no single salivary or serum constituent can accurately serve as a diagnostic marker for Sjögren's syndrome, the most important aspect of salivary diagnosis for this disease is the evaluation of the reduced quantity of saliva [8].

Multiple sclerosis is an inflammatory disease characterized by loss of myelin and by scarring resulting from the destruction/failure of myelin-producing cells by the immune system. No significant change in the saliva of these patients is noted except for a reduction in IgA production. Sarcoidosis is also an inflammatory disease of the lymph nodes, lungs, liver, eyes, skin, or other tissues that demonstrates a decrease in the secreted volume of saliva and in the enzyme activity of alpha-amylase and kallikrein [5].

Malignancy

Salivary analysis may aid in the early detection of certain malignant tumors. Tumor markers identified in saliva may be potentially useful for screening and monitoring the efficacy of treatment for malignant diseases.

The mRNA levels of specific proteins are elevated in the saliva of head and neck cancer patients. p53 is a tumor suppressor protein that is produced in cells exposed to various types of DNA-damaging stress. Inactivation of this suppressor through mutation is a frequent occurrence in the development of human cancer.

Elevated levels of salivary defensin-1 are also found to be indicative of the presence of oral squamous cell carcinoma (OSCC) [3]. Other salivary biomarkers that have been shown to be significantly altered in patients with OSCC as compared with healthy controls are inhibitors of apoptosis, squamous cell carcinoma-associated antigen, carcino-embryonic antigen, carcinoantigen, intermediate filament protein, tissue polypeptide-specific antigen, lactate dehydrogenase and IgG, insulin growth factor, and metalloproteinases MMP-2 and MMP-11 [4, 6].

A study conducted by Li et al. found a 3.5-fold elevation of seven cancer-related mRNA biomarkers in the saliva of OSCC patients. The potential salivary RNA biomarkers were transcripts of IL-8, IL-1B, DUSP1, HA3, OAZ1, S100P, and SAT, which yielded sensitivity (91%) and specificity (91%) in distinguishing OSCC patients from controls [9].

Fibroblast growth factor 2 (FGF2) and fibroblast growth factor receptor 1 (FGFR1) concentrations in saliva are significantly elevated in patients with salivary gland tumors, making it a potential biomarker in the early detection of salivary gland tumors [8].

Increased levels of recognized tumor markers c-erbB-2 and cancer antigen 15-3 (CA15-3) are found in the saliva of women diagnosed with breast cancer, as compared with patients with benign lesions and healthy controls. Higher levels of salivary nitrate and nitrite, and increased activity of nitrate reductase, were found in oral cancer patients compared with healthy individuals. There is a positive correlation between salivary and serum levels of CA125, a tumor marker for epithelial ovarian cancer [3, 6].

Infections

Diagnosis of bacterial, fungal, and viral pathogens in the saliva is based on a combination assay that measures both antibody and antigen or antibody and nucleic acid.

Mycobacterium tuberculosis can be detected in the saliva by polymerase chain reaction during the acute phase of the disease when the bacterial load is high. The presence of antibodies to other infectious organisms such as *Borrelia burgdorferi,* Shigella, *Taenia solium*, and *Entamoeba histolytica* can also be detected in the saliva. Considerable variations in the detection rate of *Helicobacter pylori* DNA in salivary samples have been observed. Detection of pneumococcal C polysaccharide in saliva by ELISA is a valuable complement to conventional diagnostic methods [3].

Salivary fungal count analysis provides valuable information in cases of oral candidiasis. The alterations in the salivary proteins, such as immunoglobulins, Hsp70, calprotectin, histatins, mucins, basic proline-rich proteins, and peroxidases, have important diagnostic value in such cases.

Certain viral diseases such as HIV and hepatitis can also be detected by sialometry. Antibody to HIV can be identified by ELISA and Western blot assay. It has been suggested that detection of IgA antibody to HIV in saliva may be a prognostic indicator of the progression of HIV infection. Orasure is the only FDA-approved, commercially available testing system that detects antibodies against the p24 antigen of HIV [5].

The confirmatory test for hepatitis virus infection is a Western (immunoblot) assay combined with a nucleic acid-based viral load assay. Herpes simplex virus type-1 (HSV-1) reactivation is involved in the pathogenesis of Bell's palsy, and PCR-based identification of virus DNA in saliva is a useful method for the early detection of HSV-1 reactivation. Salivary diagnostic tests have been designed for detection of human papilloma virus by polymerase chain reaction. For newborn infants, the salivary IgA response was found to be a better marker of rotavirus infection than the serum antibody response. Moreover, measles, mumps, rubella, and dengue fever can also be diagnosed by using saliva diagnostics [5, 6].

Monitoring hormone levels

Saliva can be analyzed as part of the assessment of endocrine disorders such as Cushing's syndrome, Addison's disease, and diabetes. Monitoring salivary testosterone levels may also be valuable for evaluating testicular function and for behavioral studies of aggression, depression, and abuse, as well as aggressive and inconsiderate behavior [4].

Monitoring drug levels

Saliva may be used for monitoring patient conformity with antipsychotic, anti-epileptic, and anticancer drugs. Other recreational drugs that can be identified in saliva are amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, and opioids. Measuring the level of salivary nicotine has proven useful in monitoring compliance with smoking cessation programs [4, 6].

Bone turnover marker in saliva

McGehee and Johnson [10] used commercially available ELISAs to test the presence of osteocalcin and pyridinoline in the whole human saliva of women [10].

Forensic evidence

Aberrant genetic material (DNA and mRNA) can potentially be recovered from saliva found on bite marks, cigarette butts, postage stamps, envelopes, and other objects in cases of crime and sexual abuse [4, 5].

Dental caries and periodontal disease

Decreased salivary flow rate and buffer capacity and increased number of *Streptococcus mutans* and lactobacilli in saliva are usually associated with a higher prevalence of caries. People at high risk for periodontal disease also carry a risk for cardiovascular and cerebrovascular diseases, making this new aspect of salivary analysis important. DNA can easily be isolated from oral epithelial cells. The loss of attachment and deepening of the periodontal pocket leads to increased leakage of a serum-like fluid, designated gingival crevicular fluid, into the oral cavity [3, 4].

Diagnosis of oral disease with relevance for systemic diseases

Quantitative alterations in saliva can be a result of 400 medications that may induce xerostomia. Qualitative changes in salivary composition can also provide diagnostic information such as increased levels of albumin in whole saliva detected in patients who received chemotherapy and subsequently developed stomatitis. Increased levels of salivary lysozyme are shown to be associated with hypertension, an early stage of cardiovascular disorders [5, 6]. Walt et al. [11] and Arregger et al. [12] reported a series of salivary markers including cortisol, nitrite, uric acid, sodium, chloride, pH, amylase, and lactoferrin that were associated with end-stage renal disease [11, 12].

Occupational and environmental medicine

Salivary biomarkers play a role in the diagnosis of occupational stress and heavy metal toxin poisoning. Increased levels of salivary cortisol and decreased levels of salivary IgA and lysozyme, saliva chromogranin A, and alpha-amylase are all markers of stress. Occupational toxins such as lead and cadmium are analyzed from the saliva. The concentration of cadmium in saliva is higher than in blood, but the level of salivary lead analysis is limited to higher levels of lead exposure poisoning [5, 6].

Conclusion

Although blood is still the gold standard medium for the diagnosis of diseases and for the detection of drugs, saliva offers a substitute to serum as a biologic fluid for diagnostic purposes. Saliva-based diagnostics is on the cutting edge of diagnostic technology and can be helpful for clinicians in the near future to formulate clinical decisions and foresee posttreatment outcomes.

Compliance with ethical guidelines

Conflict of interest

T. Khaitan, A. Kabiraj, P.T. Bhattacharya, U. Ginjupally, and H. Jha state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

References

1. Pfaffe T, Cooper-White J, Beyerlein P, Kostner K, Punyadeera C. Diagnostic potential of saliva: current state and future applications. Clin Chem. 2011;57(5):675–87.
2. Puy CL. The role of saliva in maintaining oral health and as an aid to diagnosis. Med Oral Patol Oral Cir Bucal. 2006;11:E449–55.
3. Kaufman E, Lamster IB. The diagnostic applications of saliva– a review. CROBM. 2002;13:197.
4. Mittal S, Bansal V, Garg S, Atreja G, Bansal S. The diagnostic role of saliva—a review. J Clin Exp Dent. 2011;3(4):e314–20.
5. Arunkumar S, Arunkumar J S, Burde KN, Shakunthala GK. Developments in diagnostic applications of saliva in oral and systemic diseases- a comprehensive review. J Sci Innov Res. 2014;3(3):372–87.
6. Malathi N, Mythili S, Vasanthi HR. Salivary diagnostics: a brief review. ISRN Dent. 2014;158786 (8 pages).
7. Lexner MO, Bardow A, Hertz JM, Almer L, Nauntofte B, Kreiborg S. Whole saliva in X-linked hypohidrotic ectodermal dysplasia. Int J Paediatr Dent. 2007;17(3):155–62.
8. Deepa T, Thirrunavukkarasu N. Saliva as a potential diagnostic tool. Indian J Med Sci. 2010;64(7):293–306.
9. Li Y, St John MAR, Zhou X, Kim Y, Sinha U, Jordan RCK, et al. Salivary transcriptome diagnostics for oral cancer detection. Clin Cancer Res. 2004;10:8442–50.
10. McGehee JW Jr, Johnson RB. Biomarkers of bone turnover can be assayed from human saliva. J Gerontol A Biol Sci Med Sci. 2004;59:196–200.
11. Walt DR, Blicharz TM, Hayman RB. Microsensor arrays for saliva diagnostics. Ann N Y Acad Sci. 2007;1098:389–400.
12. Arregger AL, Cardoso EM, Tumilasci O. Diagnostic value of salivary cortisol in end stage renal disease. Steroids. 2008;73(1):77–82.