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Review Article

Saliva as a Medium: A new tool in diagnosis

Deepak Narang[1], Manmeet Kaur[2], Shama Shishodiya[3], Fatima Khan[4]

[1]PG teacher Oral Medicine, Prasad Medical College Saraishazadi, Banthara, Kanpur Road, Lucknow, U.P., India
[2]Associate professor, Department of General Pathology, GGS Medical College & hospital, Faridkot, Punjab, India
[3]DNB ENT & Otolaryngology, Chacha Nehru Bal Chikitsalya, Delhi
[3]Reader OMDR, Rungta Dental College KohkaKurud (Bhillai), Chhattisgarh, India

ABSTRACT:
Saliva has been described as the mirror of the body. In a world of soaring healthcare costs and an environment where rapid diagnosis may be critical to a positive patient outcome, saliva is emerging as a viable alternative to blood sampling. As a diagnostic fluid, saliva offers distinctive advantages over serum because it can be collected non-invasively by individuals with modest training. Furthermore; saliva may provide a cost-effective approach for the screening of large populations. In the field of periodontology, traditional clinical criteria are often insufficient for determining sites of active disease, for monitoring the response to therapy, or for measuring the degree of susceptibility to future disease progression.
Key words: Saliva, oral disease, dental caries.

Corresponding Author: Dr. Deepak Narang, PG teacher Oral Medicine, Prasad Medical College Saraishazadi, Banthara, Kanpur Road, Lucknow, U.P., India

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Introduction

The second most common oral diseases next to dental caries are the periodontal diseases which are considered to be inflammatory disorder that damages tissue through the complex interaction between periopathogens and the host defence systems. Because of the increasing prevalence and associated co morbidities, screening and diagnostic modalities for the early identification of oral disease initiation and progression as well as objective measures for response to therapy, are being sought.[1]

Saliva is a clinically informative, biological fluid that is useful for novel approaches to prognosis, laboratory or clinical diagnosis, and monitoring and management of patients with both oral and systemic diseases. It is easily collected and stored and ideal for early detection of disease as it contains specific soluble biological markers. Saliva contains multiple biomarkers which make it useful for multiplexed assays that are being developed as point-of-care (POC) devices, rapid tests, or in more standardized formats for centralized clinical laboratory operations.[2]

Salivary diagnostics of common oral diseases

The physicochemical and biochemical properties of saliva along with its complex composition endowes this fluid with multiple functions, including: anti-bacterial, anti-viral and anti-fungal properties; buffering capacity for plaque acids; digestive activity (amylase, protease, nuclease enzymes) needed for food mastication; mineralizing agents for protection and repair of hard tissues; lubricant and viscoelastic properties essential for the maintenance of oral health; and protective and repairing fluid for mucosal surfaces. Saliva is a hypotonic biofluid composed of 99.5% water and 0.5% ions (e.g., potassium, calcium, chloride, sodium and phosphates), and organic micro- and macro-molecules (e.g., amino acids, histatins, cystatins, defensins, statherins, lysozyme, proline-rich proteins, carbonic anhydrases, peroxidases, lactoferrin, mucins, secretory immunoglobulins, and lipids among others).[3]

Many of the salivary or GCF derived molecules are used as diagnostic biomarkers for oral diseases including oral cancer, and conditions caused by fungi (Candida species),

viruses such as HPV, EBV, Cytomegalovirus [CMV]) and bacteria. In many instances, pathogen-induced oral diseases have been reported as opportunistic or secondary infections and are referred to as early manifestations of the Acquired Immunodeficiency Syndrome (AIDS) in HIV infected subjects.[4]

Markers affecting the dental biofilm

Specific markers Immunoglobulins (Ig) are important specific defense factors of saliva. The predominant immunoglobulin in saliva is secretory IgA (sIgA), which is derived from plasma cells in the salivary glands. Lesser amount of IgG and IgM are also found in saliva. IgA, IgG, and IgM influence the oral microbiota by interfering with the bacterial adherence or by inhibiting bacterial metabolism. There are two subclasses of IgA: IgA1 and IgA2. IgA1 is predominant in serum while IgA2 is found in higher concentrations in external secretions, that is, tears, saliva, and milk.[5]

Nonspecific markers

Mucins are glycoproteins produced by Submandibular and sublingual salivary glands and numerous minor salivary glands. The physiological functions of the mucins (MG1 and MG2) are cytoprotection, lubrication, protection against dehydration and maintenance of viscoelasticity in secretions. The mucin, MG2, affects the aggregation and adherence of bacteria and is known to interact with Aggregatibacter actinomycetem comitans and a decreased concentration of MG2 in saliva may increase colonization with this periodontopathogens.[6]

Lactoferrin is an iron-binding glycoprotein produced by salivary glands, which inhibits microbial growth by sequestering iron from the environment, thus depriving bacteria of this essential element. Lactoferrin is strongly up-regulated in mucosal secretions during gingival inflammation and is detected at a high concentration in saliva of patients with periodontal disease compared with healthy patients.[7]

Salivary Diagnostics for Systemic Diseases

Oral samples that are useful for the diagnosis of systemic diseases include saliva, gingival crevicular fluid (GCF), oral swabs, dental plaque, and volatiles. Indeed, published data indicates the successful use of all of these types of oral samples to detect or predict susceptibility to systemic diseases.[8]

The ability to accurately assess biomarkers in samples obtained from the oral cavity depends on the biochemical nature of the marker, the source and type of sample being taken, and the mechanism by which the marker enters the oral cavity. The most widely used type of oral sample is a swab that collects a deoxyribonucleic acid (DNA) sample. This has been employed for many years in forensic studies and more recently for single nucleotide polymorphisms (SNP) analyses for mutations associated with specific diseases.[9]

Salivary proteomics for existing periodontal diseases

Salivary Proteomic Biomarkers Variable amounts of blood, serum, serum products, GCF, electrolytes, epithelial and immune cells, microorganisms, bacterial degradation products, lipopolyscaaharides, bronchial products and other foreign substances are present in whole saliva. This makes saliva, the best periodontal diagnostic tool. Periodontal inflammatory mediators and tissue destructive molecules have been detected in the gingival tissues, GCF and saliva of patients affected by periodontitis.[10]

Interleukin (IL) 1β

It is a proinflammatory cytokine that stimulates the induction of adhesion molecules and other mediators which in turn facilitate and amplify the inflammatory response. Its levels correlated significantly with periodontal parameters after adjusting for the confounders.Moreover, combined levels of Il-1β and matrix metalloproteinase (MMP)-8 increased the risk ofexperiencing periodontal disease by 45 folds.[11]

MMPs

MMP-8 a key enzyme in extracellular collagen matrix degradation, derived predominantly from PMNs during acute stages of periodontal disease also correlated significantly with periodontal activity even after adjusting for the confounders, Moreover, its presence significantly increased the risk of periodontal disease.[12]

Salivary proteases as biomarkers for premalignant and malignant oral lesions

Oral squamous cell carcinoma (OSCC) accounts for more than 90 percent of oral cancers worldwide. It is particularly lethal, with a five-year survival rate post-diagnosis that hovers below 50 percent and has not improved in three decades. Its survival rates increase significantly when it is detected and treated early. Unfortunately, clinicians now lack tests which easily and reliably distinguish pre-malignant oral lesions from those already transitioned to malignancy.[13]

Detection of Systemic Cancers in Saliva

Elevated levels of the cancer antigen 15-3 (CA15-3) were detected in the saliva of women diagnosed with breast cancer compared to controls. Furthermore, in the same study, the recognised tumour marker c-erbB-2 (erb) was found to be present in the saliva of breast cancer patients and absent in control subjects, possibly representing a more robust biomarker of breast cancer than CA15-3. Another cancer antigen, CA125, which is frequently used as a serum marker of ovarian cancer, was also found to be elevated in the saliva of patients with ovarian cancer. In these studies, salivary levels were found to be a better diagnostic marker of the disease than serum values.[14]

Salivary Biomarkers in cardiovascular disease

There are numerous published reports demonstrating that C-reactive protein (CRP) can be monitored in salivary samples, however CRP remains a non-specific inflammatory response factor that increases in many conditions including periodontal diseases. Similarly salivary immunoglobulins levels are known to increase in association with coronary artery disease but once again immunoglobulins, particularly salivary IgA are elevated in response to many local and systemic conditions.[15]

Salivary biomarkers for renal disease

Aseries of salivary markers were associated with end stage renal disease. The list of markers included cortisol, nitrite, uric acid, sodium, chloride, pH, amylase and lactoferrin. In a subsequent study by these same investigators, colormetric test strips were used to monitor salivary nitrate and uric acid before and after hemodialysis. It was suggested that a salivary test could be used by patients to decide when dialysis is required, thereby eliminating unnecessary visits to a dialysis clinic.[16]

Diabetes biomarkers

Because of the large diabetic population, combined with the current epidemic of Type 2 diabetes, an oral test to monitor blood glucose would be highly desirable. Unfortunately, while it is relatively easy to measure salivary glucose, due to the multiple sources of this material in the oral cavity, salivary glucose levels do not correlate with blood glucose levels. However, several other approaches are under investigation. A recent report by Raoet al[17] demonstrated a unique proteomic signature in saliva obtained from Type-2 diabetics as compared to control saliva, with 65 proteins showing greater than a 2-fold change.

Saliva tests for forensics

Salivary test have been used for a wide variety of forensic studies. Samples can be obtained from drinking glasses, cigarette butts, envelopes, and other sources and then used to detect blood-group substances or salivary genetic proteins (primarily proline-rich protein polymorphisms). Approximately 85% of individuals secrete blood-group antigens in their saliva including A, B, H, and Lewis antigens that have been used for identification of individuals in both criminal cases and paternity law suits.[18]

Conclusion

The success of saliva as a diagnostic media is guaranteed, particularly for substances that reflect or can be directly correlated with systemic analytes. The degree of that success is likely to depend on the introduction of mobile diagnostic devices that have the capacity to measure multiple analytes in a rapid, cost-effective manner. The recent advances in oral fluid biomarker diagnostics have been fueled by novel molecular approaches and metagenomic analyses that have broadened the discovery of microbial pathogens associated with systemic and oral diseases. Similarly, these experimental approaches have been successfully used in the diagnosis of noninfectious systemic and oral conditions.

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