Medicon Dental Sciences
Volume 1 Issue 1 February 2022
Review Article

Saliva: A Diagnostic Marker in Health and Disease

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Received: January 21, 2022; **Published:** January 31, 2022

Abstract

Saliva as a diagnostic tool provides a simple, inexpensive and noninvasive tool for disease detection and screening. Saliva collection is more practical, comfortable and is highly desirable body fluid for biomarker detection in clinical applications. The role of saliva as a successful adjunct to the diagnostic parameters in various diseases and pathologies have been well documented. The article reviews the significance of various salivary markers in the diagnosis and clinical application.

Introduction

An inherent, yet profound aspect of our well-being is indicated by a miracle fluid in our body called saliva [1]. Saliva is a biofluid secreted by three major (submandibular, parotid and sublingual) and numerous minor salivary glands. Like serum, saliva also contains many biomolecules such as DNA, mRNA, miRNA, various proteins, microbes and metabolites. The term "salivaomics" was coined to emphasize its application in biomarker development and disease prognosis [2].

From a logistical perspective, the collection of saliva is simple and safe, and it may be collected repeatedly without major discomfort to the patient. Because of this, finding biomarkers in saliva inorder to detect various serious systemic illnesses, such as cancer, is of great interest for most salivary researchers [3]. This increasingly used body fluid has been recently termed "liquid biopsy", useful to detect non-oral diseases [4].

The proteins and salivary peptides can be measured using different biochemical techniques like gel electrophoresis, liquid chromatography, capillary electrophoresis and nuclear magnetic resonance (NMR) and immunoassay tests [5]. Numerous researches and experiments on "salivaomics" led to the development of a data management system called as Salivaomics Knowledge Base (SKB) [6], which is also added as web resource in supporting salivary diagnostics research [7]. Salivary miRNA isfairly more stable when compared to salivary mRNA, and the fractional change in miRNA between cancer and normal cells can be clearly demarcated.

Saliva investigation for diagnostic purposes has been proposed in the following.

1. Sjogren syndrome
2. Dental caries
3. Periodontal disease
4. Behavioral Disorders
5. Hereditary disease
6. Malignancy

7. Endocrinology
8. Viral and fungal diseases
9. Forensic Evidence

Sjogren Syndrome (SS)

Studies have shown an increase in the concentrations of sodium, chloride, IgA, IgG, lactoferrin, albumin and a decrease in the concentration of phosphate in patients with SS [8]. Proteomic analysis has also been used to distinguish between primary and secondarySS.

Dental caries

The buffering capacity, antibacterial activity, cleansing action and property of remineralization of saliva all contribute to maintaining the health of teeth [9]. Histatin S and statin levels in saliva are useful biomarkers for caries [10]. Proteins with high amounts of proline (PRP1 and PRP3), histatin1 and statin decrease in high-caries patients while the level of these proteins is high in caries-free individuals. Reports have proved a close association between dental caries and increased number of salivary microorganisms like Streptococcus mutans and Lactobacillus [11].

Periodontal disease

Elevated levels of salivary MMP-8, IL-1β and microorganism Porphyromonas gingivalis in saliva had a stronger association with moderate to severe periodontitis [12].

A marked increase in salivary level of TLR2 and 4 (toll like receptor) was seen in patients affected with periodontitis [13].

Behavioral Disorders

The application of saliva to investigate psychological phenomenon such as anxiety, depression and post-traumatic stress disorder also holds a good importance. Its primary purpose is to test cortisol and alpha amylase levels, which are indicative of stress levels. Cortisol levels rise slowly over a period of time and take a while to return to base level, indicating its association with chronic stress levels. While, alpha amylase spikes quickly and returns to baseline soon after the stress has passed, making salivary amylase measurement a potential armamentarium for studying acute stress responses [13].

Hereditary Diseases

Calcium, phosphorus, sodium, chloride, urea, uric acid, abnormal forms of Epithelial Growth Factor (EGF) and PGE-2 are elevated in the saliva of Cystic fibrosis patients. Early morning salivary levels of 17-hydroxyprogesterone (17-OHP) determined by ELISA is an excellent screening test used in the diagnosis of non-classic 21-hydroxylase deficiency.Levels of IgA Antigliadin Antibodies (IgA-AGA) are raised in the serum of Celiac disease patients and this increase is in perfect alignment with salivary IgA-AGA.

Malignancy

Increased amount of CA 125 in saliva were detected in patients with breast cancer patients as compared to healthy controls [14]. Salivary EGF was found to be significantly higher in breast cancer patients compared to healthy women [15]. Values of salivary nitrate, salivary nitrite, and activity of nitrate reductase, were found to be increased in oral cancer patients when compared with healthy individuals [16].

Elevated levels of defensin-1 and p53 antibodies can be detected in the saliva of patients diagnosed with oral squamous cell carcinoma (SCC) [17].

Endocrinology

The morning concentration of salivary cortisol aids in the diagnosis of Addison's disease and its nocturnal concentration in the diagnosis of Cushing's disease [18]. Saliva also helps in the measurement of aldosterone [19].

Viral and fungal diseases

Viral components and antibodies against viruses can be detected in saliva and hence used as a diagnostic aid for acute viral infections, congenital infections, and reactivation of infection. Orasure is FDA-approved, commercially available testing system which detects antibodies against the p24 antigen of HIV [20].

Correlation between salivary and serum IgG levels are also present in HCV antibodies, CMV (Cytomegalovirus), EBV (Epstein Barr virus), HAV (Hepatitis A virus) and Rubella virus. Salivary antibodies against poliovirus and rotavirus are reported after immunization. Therefore, salivary testing for specific antibodies is reliable method to evaluate systemic immunity in diseases or to evaluate immunity in response to vaccination [21]. Proteins like calprotectin, histatin 5, mucin, peroxidase and high proline content proteins in the saliva play important diagnostic and prognostic roles in oral candidiasis [10].

Forensic Evidence

Salivary samples obtained from bite marks, skin surface, envelopes and other objects serves as a valuable tool to detect the DNA enabling a direct link with the suspect.

Conclusion

With the recent advancements in the field of technology, saliva can be used as a reliable method in the field of dentistry, medicine, forensics, endocrinology, psychology and immune system related diseases. It goes without doubt that blood sets a gold standard when we compare the diagnosis obtained through body fluids but the advent of highly sensitive diagnostic techniques like molecular and nano technology has opened the doors for the use of salivary analysis as a promising tool in diagnosis and assessment of multiple disease processes.

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