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SALIVAOMICS– A GATE WAY TO BI DIRECTIONAL (ORO-SYSTEMIC) EXPLORATION

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ABSTRACT

Saliva has been a common fluid specimen that is important for diagnostic purpose for decades now. It can be used as a resourceful tool in the field of medicine, forensics, immune system endocrinology, psychology, dentistry, and related diseases. Lately, its use as an investigative tool has become a new normal. Saliva can be used to detect bone metabolic disorder. It performs several function like lubrication, cleaning of oral cavity also aid in deglutition and mastication process. The human saliva metabolome is a development in point-of-care diagnostic technology. In addition, Salivaomics is the study of saliva and its functions, constituents, and related techniques. Biomarkers such as growth factors, bio molecule, enzymes, and interleukins are useful in evaluating, risk, and prognosis and follow-up of disease. Saliva can be used to detect bone metabolic disorder. Along with its role in oral cavity, saliva in analyzing the levels of medicines and drugs in blood has achieved much significance. It can be used in the detection of different drugs as well as can be used as marker for viral, acute and congenital infections. The diversity of constituents in this fluid can serve as biomarkers for examining the presence or absence various systemic and local diseases. This article is about diagnostic perspective of salivary metabolome.

KEYWORDS: Biomarkers, Biofluid, Diagnostics, Salivary metabolome, Salivaomics, Saliva.

INTRODUCTION

Oral health can be predicted by saliva in the light of chemical and physical properties. Saliva is a bio fluid containing secretion of salivary glands (submandibular, sublingual, parotid and other minor salivary glands). Body consists of different fluids such as blood, urine, mucosal cell and saliva all of which include proteins that are linked with several systemic and oral disorders.[1] Human saliva is part and parcel of teeth and oral mucosa as it emotes a vital part in the maintenance of oral hygiene. Saliva acts as a line of defense against different pathogens. It contains 99% water and various electrolytes that include magnesium, phosphate, bicarbonate, mucin, proteins, nitrogenous products and immunoglobulin. A healthy individual secretes an average of 0.5ml/min and 500-1500ml of saliva per day[2].[2,3] Furthermore, saliva is multifunctional; it also poses antiviral, anti-bacterial and anti-fungal properties.[4] According to the state of body, salivary composition can vary and under pathological and physiological state salivary constituents can be altered. It performs several function like lubrication, cleaning of oral cavity also aid in deglutition and mastication process.[5,6] Moreover, a relationship between saliva and serum parameters have been found in studies hence while detecting changes in the body it can be used. The aim of this review is to find out the role of salivary biomarkers in diagnosis of disease and other clinical applications.

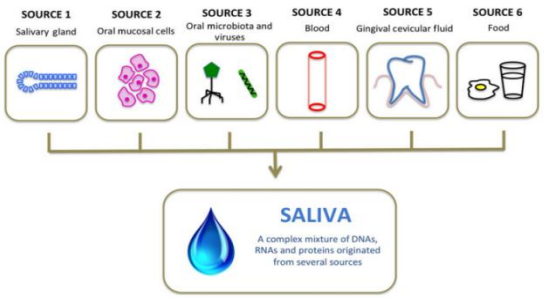

Figure 1: Saliva can be extract from following resources.[7]

Salivaomics

Saliva-omics is the study of saliva and its functions, constituents, and related techniques.[8] It includes various bio molecules that contain micro-biota, DNA, proteins, metabolites, mRNA and micro RNA. In 2008 the phrase "saliva-omics" was discovered to highlight its use in the development of biomarker where "omics" is the study of biological molecule. Saliva omics comprise of proteome, metabolome, transcriptome (mRNA, microRNA and other non-coding RNAs), genomics (human and microbial), oral micro biome, and epigenome (DNA methylation).[9,10] Bio sensor has been used for measuring the salivary levels of oncologic markers, microorganisms, metabolic compounds and several drugs has opened the door for the study of clinical salivary diagnostics and interactions of host–pathogen mechanism.

Emerging Role of saliva

Salivary Bio-markers

Saliva can be used for the diagnosis of oral and systemic diseases. It has serum constituents and molecules that give important information that can be used for application of diagnostic purpose.[11] Biomarkers such as growth factors, bio molecule, enzymes, and interleukins are useful in evaluating risk, prognosis and follow-up of disease. Further studies need to be conducted to find new biomarkers and their roles in the diagnosis.[12]

Sjögren's Syndrome

Sjorgen's syndrome is a systemic autoimmune disease, associated with disorders of endocrine system along minimized secretion of lacrimal and salivary glands.[13] **Primary sjogren syndrome:** a disease that damages the lacrimal and salivary glands. The mechanism is based on B lymphocytes hyperactivity, representing an enhancement in T lymphocyte mediated antibody production and interferon production pathway activation.[14] The destruction of glands can create an inflammatory response in salivary glands resulting in "Xerostomia". It can also be associated with diverse complications such as caries, periodontal disease and candidiasis.[15] Further studies have revealed that patients with Sjogren's syndrome has increased concentration of IgA, IgG, albumin, lactoferrin and NaCl levels where as phosphate levels were low. Furthermore, Analysis of salivary protein revealed that levels of cystatin C, beta 2 micro globulin, and lysozyme C levels were high in patients with sjogren syndrome whereas carbonic anhydrase and salivary amylase were low. Primary and secondary sjogren syndrome can be differentiated by using proteomic analysis.[16]

Bone Turnover Markers

Saliva can be used to detect bone metabolic alterations. Saliva in humans was analyzed for osteocalcin (OC) and deoxypyridinium (D-PYR) and association between OC concentration, 3 calcaneus T scores, age, body mass index and D-PYR. It has been observed that for analyzing human biomarkers of bone turnover, saliva could be used as a fluid. A positive alliance between salivary concentrations of hepatocyte growth factor, alveolar bone loss and interleukin-1 beta was observed. On the other hand no link has been found between salivary osteonectin and alveolar bone loss.[17,18]

Cardiovascular Disease

In myocardial infarction (MI) patient's salivary biomarkers such as creatinine kinase myocardial band (CKMB), cardiac troponins (cTn), C-reactive protein (CRP), myoglobin (MYO), and myeloperoxidase, when used in grouping with an ECG shows positive association in contrast to healthy individuals. In AMI (acute myocardial infarction) patients, salivary MYO levels are notably raised in 48 hour of onset of chest pain. Troponins and CK MB with poor diagnostic ability are also detected in saliva.[19] According to Miller *et al*, in AMI patient, salivary concentrations of MMP-9, TNF-α and CRP were raised along with elevated levels of salivary soluble ICAM-1 (Intercellular Adhesion Molecule-1, also called CD54, in human encoded by ICAM-1) and myeloperoxidase. However, CD40 level were low in those patients.[20] At initial stage of CVD (cardio vascular diseases) high level of salivary lysozyme are associated with hypertension.[21,22]

Dental Caries and Periodontal Diseases

Saliva plays important role in oral cavity as it helps to detect the quality and quantity of oral bacteria. More number of Lactobacilli and Streptococcus mutants in saliva are allied with increased caries prevalence and root caries.[11] In moderate to severe periodontitis, elevation of IL-1 β, microorganism Porphyromonas gingivitis and MMP-8 had strong relationship.[23] Elevated levels of alkaline phosphatase and aspartate amino transferase are associated with periodontal disease and can be used as marker for it. In periodontitis and diabetic patients, albumin and uric acid levels are low in saliva due to oxidative stress.[24] The salivary expression of CA VI (carbonic anhydrase-vi), IL-1Ra (interleukin -1 receptor antagonist) Arp 3 (Actin related protein) and pIgR (polymeric immunoglobulin receptor) was down-regulated, where as in patients with Type 2 diabetes mellitus following agents LEI (leukocyte elastase inhibitor), IGJ (protein immunoglobulin J) and PLS-2(plastin-2) were up-regulated.[25]

Diseases of the Adrenal Cortex

Morning saliva is aids to diagnose Addison's disease, whereas nocturnal concentrations of saliva are used to diagnose Cushing's syndrome.[26,16]

Drug Level Monitoring

Saliva has gained popularity for monitoring bioavailability of drugs. It can be used in the detection of diazepam's, amphetamines, and ethanol nicotine, cannabinoids, cocaine, phencyclidine, opioids, barbiturate presence. In the saliva unbound concentration of the drugs gets diffuse into it and is measured with reproducibility. The evaluation of illicit drug use is

another most necessary diagnostic application of saliva. Bioavailability of drug takes place at the same time in both specimen (serum, saliva), hence its show novelty for forensic findings too.[27,28]

Forensics

Saliva can be used for forensic for which the samples can be taken from food products, glasses, skin surface, and additional sources as well. DNA can also be tested via salivary sample.[29]

Genetic Disorders

Cystic Fibrosis

It's a disorder that affects the lungs, digestive system and other organs as well. It is caused by alteration in the gene CFTR (cystic fibrosis trans-membrane conductance regulator). Modified saliva was observed in CF (Cystic fibrosis) patients. In saliva of CF patients, the level of activity of cathepsin-D was considerably raised as compared to healthy controls before excretion's spur with paraffin pledget.[30] In the saliva of cystic fibrosis patients, level of phosphorus, sodium, chloride, calcium, uric acid, urea, abnormal forms of Epithelial Growth Factor (EGF) and PGE-2 (prostaglandin E2) were found. As compared to healthy individuals, lactate dehydrogenase levels, magnesium concentration and salivary calcium concentration were high among CF patients.[31]

Ectodermal Dysplasia

X-linked hypohidrotic ectodermal dysplasia (HED) is one of the most common types of genetic disorders. According to the study conducted by lexner *et al* reported that in male and female carrier hypohidrotic ectodermal dysplasia (HED) affected the whole saliva flow and composition and concluded that levels of inorganic components and protein profile were significantly higher. On the other hand, in saliva alpha amylase found to be low.[32]

Infections

A mixture of IgA, IgG, IgM, is obtained in Oral mucosal transudate (OMT), a rich source of antibodies. In saliva, measles virus specific IgM was found. According to a study performed by Oliveira *et al*.,[33] Saliva can be used as marker for viral, acute and congenital infections. Their antibodies and viral components against viruses can be found in saliva. According to FDA Orasure detects antibodies against the p24 antigen of HIV.[16] In HCV antibodies, CMV (Cytomegalovirus), EBV (Epstein Barr virus), HAV (Hepatitis A virus) and Rubella virus, association between salivary and serum IgG was found. Hence salivary testing for specific antibodies is a reliable method to evaluate systemic immunity in diseases or to evaluate immunity in response to vaccination.[34] In prognosis and diagnosis of oral candidiasis salivary proteins such as, peroxidase, histatin5, mucin, calprotectin, and elevated proline content plays a significant role.[35,16]

Covid19

SARS-CoV-2 infection apart from systemic manifestations is associated with local, oral cavity signs and symptoms such as dysgeusia, dry mouth, taste loss as well as mucosal lesions (ulcerations, enanthema and macules) in about half of Covid-19 individuals.[36] Its Virus can spread into the body through direct and indirect contact, saliva was found to be the commonest route. Saliva might be considered as the other substitute for screening SARS-CoV-2 infections and check viral load. Through different routes SARS- Cov-2 is found in saliva. In covid19 patients, presence of salivary gland infection can be indicated by saliva. Salivary specimen not only includes secretion of major and minor salivary gland but also secretion from nasopharynx or lung through airways lined by cilia, through GCF SARS-CoV-2 in the blood can reach the oral cavity. Further studies are required to find out the sources of covid19 in saliva and its influences on the spread of virus.[37,38,40]

Future Recommendations

It is recommended to conduct further studies to find mechanism of action for salivary biomarkers. Saliva is a self-collecting fluid that can be collected and transferred to the laboratory where it can be tested non-invasively and especially easily accepted by small children/elderly patients and differently-abled people for whom nasopharyngeal sample collection is not acceptable. Furthermore, researches need be conducted using gold standard biomarkers to analyze systemic condition at different stages for management and prevention of condition. Focus must be drawn for utilizations of salivary metabolome as objective clinical tool for disease screening purpose.

CONCLUSION

Saliva is an essential biofluid and has numerous biomarkers that can be used for diagnostic purpose. It has a profound effect on oral health, with the advancements in technology, this bio fluid can be utilized in the field of forensics, psychology, immune system related diseases, endocrinology and medicine as a diagnostic tool and it also has several other benefits like processing collection and sampling is quick and noninvasive. It also simplifies a patient's ability to take recurring samples for long-term disease monitoring, also reduces the pain and anxiety that is naturally associated with blood tests.

Clinical significance

Saliva possesses protein and nucleic acid that speculate bodily functions moreover saliva is quite reasonable in contrast to other body fluids and possess a high potential to reform the next generation of diagnostics.

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