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SAILOCHEMISTRY IN DISEASES: A REVIEW

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ABSTRACT Saliva lac	ks the drama of blood, sincerity of sweat and emotional appearance of tears', but, still the fact is that it is the

explored for health. Advances in the use of saliva as a diagnostic fluid have been tremendously affected by current technological developments. In this paper we have focused more on systemic disease which may help us in identifying the diseased with the help of saliva. In future it may help us in knowing the condition with help of markers in the saliva which help in the management.

KEYWORDS: saliva, markers, proteinomics and immunoglobulins.

Introduction

SALIVA is an exocrine secretion and its components being dispensed into the ducts. Saliva which has been used in basic physiological functions like mastication, have now shown to play a vital role in diagnosis of various oral diseases like oral cancer, and HIV and as well in the diagnosis of numerous systemic diseases like, Diabetes, Heart diseases, etc and hence is considered as the Magic mirror of health. Saliva is a unique fluid and interest in it as diagnostic medium has advanced exponentially in the last 10 years.¹

Saliva offers distinctive advantage over serum because it can be collected non invasively by individuals with modest training. No special equipment is needed for collection. It is a cost-effective approach for the screening large population. It is useful for diagnosis of hereditary disorders, autoimmune disease, malignant and infectious diseases & endocrine disorders as well as in the assessment of therapeutic levels of drugs and monitoring of illicit drug use.

Composition of the saliva:

99.5% of saliva is water and the rest is solid electrolytes- K+, Na+ and bicarbonate ions, organic matter like amylase, lysozymes, mucin and acid, H_2CO_3 are important. Calcium, urea, free amino acids and immunoglobulins parotin & Nerve growth factor are other factors that present in the saliva.² Saliva contain 1166 proteins. Using salivary transcriptome as a diagnostic tool, a set of 185 mRNA was identified as normal salivary core transcripts. (table 1)

Substance	Function
Amylase	Starch spitting enzyme
Lysozyme	Causes lysis of many common bacteria
Mucin	Lubricating material and makes the food slippery-Facilitates swallowing of the food
Immunoglobulins	Acts against various bacteria
Parotin	Local hormone and not much is known about it. This probably helps in calcium deposition in the teeth
Nerve Growth factor (NGF)	Help the growth of sympathetic ganglion
H ² CO₃ and bicarbonates	Ph of the saliva depends on the ratio of H_2CO_3 and $NaHCO_3$

Table 1: substances of saliva along with the functions

COLLECTION OF SALIVA

Gland specific Saliva can be collected directly from individual salivary glands. This is useful for detection of gland-specific pathology like infection & destruction. For evaluation of systemic disorders, whole saliva is most frequently used.

Whole saliva means is a mixture of oral fluids and includes secretions from both the major & minor salivary glands, non salivary origin-GCF, expectorated bronchial and nasal secretions, serum & blood derivatives from oral wounds, bacterial and bacterial products, viruses and fungi, desquamated epithelial cells, other cellular components and food debris. Saliva is collected with or without stimulation.

Stimulated saliva is collected by gustatory stimulation/ masticatory action. Un stimulated saliva is collected without exogenous gustatory, masticatory or mechanical stimulation.

Unstimulated salivary flow is most affected by the degree of hydration, but also by olfactory stimulation, exposure to light, body positioning and seasonal and diurnal factors. Main method of whole saliva collection is by **draining**, **suction**, **splitting**, **and absorbent** (**sponge) methods**.

Sailochemistry in Diseases:

Saliva is a mixture of ions, small organic molecules, enzymes, and proteins, some in multi protein complexes and others complexes with bio-chemicals. In addition to this, the oral microorganisms and their byproducts, create an ecological system that either maintains good health or, conversely, contributes to its decline. Saliva is vital to the integrity of the teeth as well as the soft tissues.³

Dental caries

Clinically significant decrease in salivary flow can be considered as an etiologic factor that contributes to the development of dental Caries. Salivary parameters such as salivary flow rate, salivary viscosity, salivary pH and salivary buffering capacity were lower in subjects with high dental caries. Hence, we recommend salivary testing to be a part of routine diagnosis when treating patient with high dental caries risk.

Periodontitis:

Several enzymes that are evaluated for the early diagnosis of periodontal disease are aspartate and alanine aminotransferase (AST, ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), alkaline and acid phosphatase (ALP, ACP), and gamma glutamic transferase.

Cystic fibrosis:

Cystic fibrosis (CF), transmitted by a single autosomal recessive gene, affects 1 in 2500 of the population. A biochemical abnormality affects the quality of mucus, and results in pancreatic duct obstruction, and progressive lung damage as a result of respiratory infection. In one study done by Sagers et al. in 1967 it was found that there was a clear distinction between the sodium levels in normal and heterozygotes on the one hand, and cases of CF on the other⁴

Elevated levels of calcium phosphate and proteins in subma ndibular saliva from CF patients were found, and resulted in a calcium protein aggregation which causes turbidity of saliva. The submandibular saliva of patients who also found to contain more lipid than saliva of non-affected individuals neutral lipids, phospholipids and glycolipids are elevated. Elevations in electrolyt es sodium, chloride, calcium and phosphorus, urea and uric acid and total proteins were observed in submandibular saliva of CF patients. Minor salivary glands also affected –elevated levels of sodium and a decrease in flow rate were reported for their glands in CF patient.⁴

Coeliac Disease:

It is a congenital disorder of the small intestine that involves malabsorption of gluten. Serum IgA anti gliden antibodies (AGA) are increased in patients with coeliac disease and dermatitis herpeti formis. Many authors have found that antibody levels in saliva and serum in untreated celiac disease were significantly higher than in other groups. Alpha-gliadin antibodies appeared to be a better discriminator for serum but not for saliva. The assay of salivary IgA antibodies to gliadin offers a non-invasive test which would be particularly useful in the investigation of celiac disease and for monitoring compliance with a gluten-free diet.⁴

21-Hydroxylase Deficiency

2 1-Hydroxylase Deficiency, (21-OH Deficiency) represents the most common form of Congenital Adrenal Hyperplasia (CAH), a complex and heterogenous group of conditions, characterized by defects in one of the five enzymes involved in adrenal steroidogenesis. Early morning salivary levels of 17-hydroxy progesterone (17-OHP) were reported to be an excellent screening test for the diagnosis of nonclassic 21-hydroxylase deficiency, since the salivary levels accurately reflected serum levels of 17-OHP. High correlation (r=0.93) between salivary and serum concentrations of 17-OHP was observed in both affected and healthy individuals.¹

Sjogren's Syndrome:

SS is a chronic, multisystem, autoimmune disorder. Specific antinuclear antibodies, the SS-A (Ro) and SS-B (La) antibodies, are found in Sjogren's syndrome and may have diagnostic value in patients with unexplained parotid swelling or other features such as renal and pulmonary lesions. Salivary duct auto antibodies are another characteristic finding in this disease, but it appears that these antibodies may be causally unrelated to the duct damage.⁵

Juvenile Idiopathic Arthritis

Arthritis is defined as either joint swelling (effusion, synovitis, periarticular joint swelling or bone expansion) or at least three of reduced range of movement; tenderness or pain on movement; warmth of the skin and muscle spasm.⁷ The results highlight that the unstimulated and stimulated flow rates for the JIA patients are significantly lower than controls. This in turn may imply a reduced salivary buffering capacity due to both a reduced salivary volume, and reduced bicarbonate levels.⁷

Diabetes Mellitus

Serum and salivary glucose was assayed by the use of an enzymatic colorimetric test kit, GOD-PAP (Plasmatec, U.K.). The salivary glucose concentration showed a parallel increase with an increase in the serum glucose concentration. In oral cavity, albumin is regarded as a serum ultra-filtrate to the mouth.⁸ Salivary albumin is increased in medically compromised patients whose general condition geting worse. Albumin is often used as a marker for the degree of mucositis

or inflammation in the oral cavity. No significant difference in salivary albumin was found between type1 diabetic patients and control group. The salivary albumin of type 2 diabetic patients was significantly higher in comparison with control group. ⁸ Oxidative stress is increased in diabetes, because of excessive production of reactive oxygen species (ROS) lipid peroxide in the blood provides useful information for the prognosis of diabetes in which secondary disorders are often fatal. Exploring saliva for oxidative stress and antioxidant markers that accurately reflect the redox status of the body may have great clinical interest.

The cholesterol and triglyceride concentra-tions in serum and saliva were substantially increased in the diabetic group as compared with the control group. The concentrations of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) were significantly high and the concentrations of HDL-C were significantly low among diabetics.⁹

The serum and salivary MDA levels, a product of lipid peroxidation, is increased significantly among diabetics. Antioxidant activity was assessed in this study through measuring the concentration of US, SOD and GSH reductase in the serum and saliva of diabetic and control groups. The detection of increases in UA levels in saliva should alert clinicians to the commen¬surately increased vulnerability of the diabetic patient to life-threatening cardiovas cular complication.¹⁰

Epilepsy

Several recent studies have reported good linear correlations between phenytoin concentrations in mixed saliva and those in serum, cerebrospinal fluid, and plasma. These studies suggest that phenytoin in saliva may be in equilibrium with the free therape utically active phenytoin in plasma water. With the exception of Reynolds et al. (1976) who reported a 6% decrease in salivary phenytoin concentration after stimulation, the effect of exogenous stimulation on salivary concentration was not investigated.¹¹

Cardiovascular Diseases

Markers in saliva may be useful in postoperative follow up among patients undergoing cardiovascular surgery. Determinations of total serum amylase and salivary amylase activity have been made before and 6 h after cardiovascular surgery. The results indicated that if salivary amylase levels were low in preoperative patients with ruptured aortic aneurysm, there was an associated increase in mortality (Adam et al, 1999).¹

Renal Diseases

Salivary creatinine concentrations show a high sensitivity and specificity for determining the presence of renal disease (Lloyd, Broughton and Selby, 1996).¹² **Nitrite and uric acid**, that act as biomarkers in saliva to indicate the need for dialysis in patients who have renal disease. The investigators are developing **colorimetric dipstick tests** that patients can use at home to track their uric acid and nitrite levels in saliva and determine when they need dialysis treatment.¹³

Oral squamous cell carcinoma:

OSCC patients, if the saliva contains the shedding tumor cells originating from OSCC tissues, the detection of tumor markers in saliva would be potential clinical value on early detection, early diagnosis and prognostic monitoring. Actin and myosin were the most promising protein biomarkers identified in the saliva. Both proteins displayed increases in their abundance levels in soluble saliva from subjects with malignant lesions compared to those with pre-malignant lesions.¹⁴ The positive rate of telomerase activity in saliva from OSCC patients was 73.53% (25/34), which was significantly higher than that from healthy persons with 6.67% (2/30). There is some prognostic value on detection of preoperative saliva Cyfra 21-1 concentration and telomerase activity for their increase in the OSCC patients with tumor recurrence. Cyclin D1 gene amplification has been found to be associated with poor prognosis

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in OSCC. In another study Ki67 markers were increased, while 8oxoguanine DNA glycosylase, phosphorylated-Src and mammary serine protease inhibitor (Maspin) were found decreased in the saliva of patients with OSCC. Microsatellite alterations of DNA were also observed in the saliva of patients with small cell lung cancer.¹⁴

Breast Carcinoma

Elevated levels of recognized tumor markers-C-erb B-2 (erb) and cancer antigen 15-3 (CA15-3) were found in the saliva of women diagnosed with **breast carcinoma.** But c-erb- B-2 was not detected in healthy subjects- thus appears to hold greater promise for the early screening of breast cancer. Certain proteins would be elevated in the saliva of patients with breast cancer. The levels of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and arcinoembryonic antigen (CEA) in the saliva were measured with enzyme-linked immunosorbent assay (ELISA).

Drug Monitoring: Cotinine a major metabolite of nicotine, has a longer half-life approximately 16 hours and its concentration in plasma and saliva has been used as a marker of nicotine intake in adults. Saliva cotinine was measured by capillary gas chromatog raphy and nitrogen selective detection.¹⁶

HIV

Distinct from other mucosal sites (eg: genital tract) the oral cavity is rarely a site of human immunodeficiency virus type 1(HIV-1) transmission despite detectable amounts of RNA, proviral DNA and infected cells from the saliva or from the oropharyngeal tissue of HIV infected patients. Antibody to HIV in whole saliva of infected individuals which was detected by ELISA and Western blot assay corrugated with serum antibody levels. IgA levels in the saliva decrease/decline if the patient becomes symptom atic. Analysis of salivary antibody specific for HIV as a diagnostic test has advantage when compared with serum.

Saliva collected non-invasively, which eliminate the risk of infection for the health care workers. **Ora Sure** is a testing system that commercially available. Test depends on oral mucosal transudate IgG antibody is predominant type of anti-HIV immunoglobulin.¹⁷

Acute hepatitis A (HAV) and hepatitis B (HBV) were diagnosed based on the presence of IgM antibodies in saliva. Analysis of oral fluid samples collected with "oral sure" provides an excellent method for the diagnosis of viral hepatitis B and C.¹⁸ Rota virus infection in neonatal elicits specific mucosal antibody response which persisted for at least 3 months. The shedding of herpes virus is common in infected individuals. In Bell's palsy patients, identification of virus in saliva is useful method for the early detection of HSV-1 infection. Dengue is mosquito - transmitted viral disease. Salivary levels of anti-dengue IgM and IgG demonstrate 92% sensitivity & 100% specificity in the diagnosis of primary or secondary infection. A new multiplex nested PCR technique can be used with saliva to detect and type lymphotropic herpes viruses including Epstein-Barr, cytomegalovirus, human herpes virus 6.7 and 8. A new Epstein-Barr virus (EBV) capsid antigen antibody capture radioimmunoassay with saliva is apparently useful in epidemiological studies of EBV in school children.

CONCLUSION

Saliva collection allows the measurement of analytes in multiple samples collected at home or in remote locations. The only salivary kits that are FDA approved at this time are those associated with the Ora Sure for HIV and drugs of abuse (Epitope), although kits for steroid hormones and secretary Ig A and melatonin (ALPCO) are available for research use may be submitted for FDA approval in the near future. We can diagnosis different systemic disease through saliva, which is easily available, can be collected easily and it is a noninvasive technic. In near future it can be a definite medium for diagnosing the diseases and knowing their prognosis.

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