

“Salivary Diagnostics” – A Review Article

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ABSTRACT: *Saliva Is Abundantly Delivered Within The Mouth And Saliva Collection Is A Relatively Easy Procedure. Therefore, Saliva Evaluation Might Be Considered As A Possible Alternative To Blood And/Or Tissue Analyses, For Researching Specific Molecule Associated To The Presence Of Systemic Diseases, Oral Diseases And Malignancies. Salivary Diagnosis Is Viewed As A Promising Modality That Can Provide An Early And Accurate Diagnosis. Saliva Has Several Advantages Over Serum And Tissue Fragments In Its Use As A Diagnostic Tool.*

Keywords; *Saliva, Salivary Diagnosis.*

1. INTRODUCTION

The Detection Of Protein Levels In Biological Fluids Is Well Studied And Considered A Crucial Diagnostic Method For The Identification Of Diseases. Body Fluids Provide A Good Perspective Regarding The Biological Processes And Therefore The Health Of Various Organs. The Physical Body Consists Of A Variety Of Fluids, Like Blood, Urine, And Saliva, With A High Quantity Of Proteins That Can Be Related To Several Systemic And Oral Diseases. These Fluids Proved To Have Found Widespread Clinical Applications So As To Diagnose And Monitor Human Health. One Of The Foremost Appealing Diagnostic Tools Is Assumed To Be The Human Saliva, Holding The Key To An Early Diagnosis, A Far Better Treatment, And An Improved Prognosis ^[1].

The Term “Precision Medicine” Refers To The Uses Of Molecular Profiles, Genomic, Transcriptomic, Proteomic And Metabolomics, To Adapt A Personalized Therapeutic Strategy For Peculiar Patients: A. In The Right Moment, B. To Determine The Predisposition To Diseases, And C. To Provide Timely And Targeted Prevention ^[2]. The Combination Of Such Profiles And Therefore The Identification Of Biomarkers Is Resulting In The Event Of Latest Technologies, Supported Easy And Non-Invasive Methods To Gather Diagnostic Human Specimens, Possibly With A High Specificity And Sensitivity And Customized On Single Patient ^[3].

One Of The Foremost Appealing Diagnostic Tools Is Assumed To Be The Human Saliva, Holding The Key To An Early Diagnosis, A Far Better Treatment, And An Improved Prognosis ^[1]. Systemic Diseases Are Very Challenging To Diagnose Without More Invasive Supplementary Investigations. In Order To Beat This Condition, Medical Researchers Worked Into Finding Molecular Disease Biomarkers Which Will Be Easily Identified And Where They Will Successfully Implement A Non-Invasive And Fast Diagnosis ^[1].

Saliva

The Whole Saliva Consists Of The Secretions Of The Minor And Major Salivary Glands Also As Mucosal Transudations, Gingival Crevicular Fluid, Serum And A Few Blood Derivatives, Desquamated Epithelial Cells, Bacteria, Viruses, Fungi, And Food Debris. Saliva Could Also Be A Posh Fluid That Also Contains A High Number Of Hormones, Proteins, Enzymes, Antibodies, Cytokines, And Antimicrobial Constituents Which May Facilitate Their Associations With A Variety Of Systemic Diseases ^[1]. The Salivary Fluid Is An Exocrine Secretion That Consists Of Roughly 99% Water, With A Spread Of Electrolytes (Sodium, Potassium, Calcium, Magnesium, And Phosphate), Proteins Like Enzymes, Immunoglobulins, Antimicrobial Factors, Albumin, Polypeptides And Oligopeptides, Traces Of Albumin, And Mucosal Glycoproteins Of Great Importance In Maintaining A Balance Of The Oral Health. Saliva Also Contains Glucose, Urea, And Ammonia In Various Quantities That Can Interact And Be Responsible For Several General Diseases ^[9].

Salivary Diagnosis

Saliva Is Abundantly Delivered Within The Mouth, Its Collection Being Simple And Non-Invasive. Moreover, Transportation And Storing Are Easy. For Such Reasons, Saliva Evaluation Might Be Considered As A Possible Alternative To Blood And/Or Tissue Analyses, For Researching Specific Molecules (DNA, RNA, Proteins And Metabolites) Associated To The Presence Of Systemic Diseases And Malignancies ^[4]. Saliva May Be A Unique Fluid That Contributed To The Event Of A Brand-New Diagnostic Tool Within The Past Few Years. It Is Said That Saliva Reflects The “Body’s Health” And Well-Being, But Until Recently Its Use As A Diagnostic Tool Has Been Hindered Because The Examination Of The Biomolecules That Exist In Saliva And Their Relevance And Association With Different Aetiologies Has Been Not Enough Explored ^[7]. Salivary Diagnosis Is Viewed As A Promising Modality That Can Provide An Early And Accurate Diagnosis, An Improved Prognosis, And An Honest Monitoring Post-Therapy. The Assay Of Saliva Represents A Good Area Of Research At This Point And Has Implications That Focus On Basic And Clinical Purposes.

Saliva Has Several Advantages Over Serum And Tissue Fragments In Its Use As A Diagnostic Tool. One Of The Most Appealing Characteristics Is The Non-Invasive Approach That, Combined With The Easy Collection Method And Storage, Makes It A Valuable Tool. New Technologies Have Proven Their Efficacy And Unveiled An Outsized Number Of Salivary Biomarkers That Are Connected To Many General And Oral Diseases ^[6].

Used For The Diagnosis Of Systemic Diseases, Saliva Is A Crucial Advantage, Primarily Because Saliva Contains A Little Amount Of Plasma. Plasma-Derived Biomarkers In Saliva Facilitate The Continual Monitoring Of The Oral And General Health Status ^[8]. Saliva Contains A Set Of Analytes, Like Proteins, DNA, Mrna, Several Metabolites Which Will Be Potential Biomarkers For Clinical And Translational Applications ^[12]. Moreover, Saliva Contains A Wide Range Of Benefits As A Clinical Investigation Tool Compared With Blood Serum And Tissues. The Sample Collection Handling Required No Special Equipment, Simple Storage With No Clotting And Shipping, Cost-Effective, Easily Available In Large Volumes For Analysis And Repetition And Monitoring Over Time Is Also Quick And Easy^[13].

Sialochemistry

There Are 3 Major Salivary Glands (Parotid, Submandibular, Sublingual) And Several Minor Salivary Glands (Labial, Buccal, Palatal) Which Contribute To The Secretion Of

Saliva. Abnormal Proteins Are Also Produced Under Certain Conditions, Such As Tumors And Nutritional Deficiency. Low Amylase Concentrations Are Seen In Cases Of Starvation And After Destruction And Degeneration Of The Acinar Cells. Elevated Amylase Is Seen In Abnormal Water Loss In The Ducts ^[39].

Sialo-Chemistry Are Often Expected To Reveal The Differentiation Between Normal And Abnormal Function Of The Glands, Information About Gland Dysfunction And Its Impact On The Oral Environment, Clues To Homeostatic Fluctuations As A Result Of Circulatory, Innovatory, Or Hormonal Adjustments ^[41]. Saliva Is Increasingly Being Used As An Investigational Aid In The Diagnosis Of Systemic Diseases That Affect The Function Of The Salivary Glands And The Composition Of The Saliva, Such As Sjogren's Syndrome, Alcoholic Cirrhosis, CF, Sarcoidosis, DM And Diseases Of The Cortex. In The Past 10 Years Researchers Have Demonstrated That Saliva Tests For Anti-Bodies To HIV Represent A Non-Invasive Alternative To Quantification Of Antibodies In Blood For Monitoring The Efficacy Of Antiretroviral Therapies And Disease Progression To Acquired Immunodeficiency Syndrome ^[42].

Salivary Biomarkers Used In Diagnostics

Saliva May Be A Complex Bio Fluid With An Emerging Role To Research Circulating Cancer Biomarkers That Presents A Far Better Specificity And Sensitivity In Terms Of Diagnosis, Prognostication, Monitoring, And Treatment Of Diseases. Saliva Has An Edge Over Other Body Fluids By Having A Low Background Of Inhibitory Substances And Normal Material, Which Shows Less Complexity Compared With Blood ^[11].

Streckfus Et Al. Reported The First Salivary Biomarker Her2/Neu For Breast Carcinomas And Also Reported The Increase In The Level Of CA15-3 ^[14], ^[15]. Schapher Et Al. Suggested The Higher Levels Of Salivary Leptin In Salivary Gland Tumors ^[16]. Chen Et Al. Described The Salivary CA 125 To Be Elevated In Ovarian Cancer Patients. Wong Et Al. Identified Mrna Biomarkers In The Patients Of Pancreatic Cancer ^[17]. At An Early Stage Of Gastric Cancer, The Salivary Proteomes May Identify The Cancer ^[18]. Thus, Salivary Analysis Is An Effective Option For The Prevention, Monitoring, Diagnosis, And Prognosis. ^[19].

Salivary Analysis Are Often Valuable To Discriminate And Monitor Swellings Of Major Salivary Glands Like Chronic Recurrent Parotitis, Where The Blood-Saliva Barrier Is Violated Within The Inflammatory Flare-Ups And Characterized By The Leakage Of Serum Components (Albumin) And Lactoferrin Into Saliva ^[40]. Abnormal Proteins Are Also Produced Under Certain Conditions, Such As Tumors And Nutritional Deficiency. Low Amylase Concentrations Are Seen In Cases Of Starvation And After Destruction And Degeneration Of The Acinar Cells. Elevated Amylase Is Seen In Abnormal Water Loss In The Ducts ^[39].

In Oral Health And Therefore The Dental Sciences, Use Of Salivary Biomarkers And Proteomic Analysis Can Each Have A Crucial Role To Play Within The Understanding Of Varied Oral Diseases, Including Caries ^[20], Periodontitis (Aggressive/Chronic) ^[21], Sjogren's Syndrome ^[24], Behcet Syndrome ^[22], Oral Leukoplakia ^[23], And Carcinomas Particularly In The Head And Neck Region ^[25].

There Are Numerous Published Reports Demonstrating That C-Reactive Protein (CRP) Are Often Monitored In Salivary Samples, However CRP Remains A Non-Specific Inflammatory Response Factor That Increases In Many Conditions Including Periodontal Diseases ^[43]. Elevated Salivary Lysozyme Levels, A Biomarker For Oral Infection And Hyperglycemia, Has Also Shown A Significant Association With Hypertension, An Early

Stage Of Cardiovascular Diseases. ^[44]. Salivary Phosphate Has Been Successfully Used As A Clinical Biomarker For Hyperphosphatemia, Which Is An Important Contributor To Cardiovascular Calcification In Chronic Renal Failure (CRF) ^{[27] [28] [38]}. Pain Responses In Dental Pulp Are Specifically Related To Neuropeptides Including Calcitonin Gene-Related Peptide (CGRP), Substance P, Neurokinin A And Neurokinin P. Salivary Testosterone Levels Have Been Associated With Increased Aggressive Behaviour And Also With Athletic Activities^[5]. Salivary Test Are Used For A Good Sort Of Forensic Studies. Samples Are Often Obtained From Drinking Glasses, Cigarette Butts, Envelopes, And Other Sources Used To Detect Blood-Group Substances Or Salivary Genetic Proteins (Primarily Proline-Rich Protein Polymorphisms). Many Of The Salivary Or GCF Derived Molecules Are Used As Diagnostic Biomarkers For Oral Diseases Including Carcinoma, And Conditions Caused By Fungi (Candida Species), Viruses And Bacteria.

Among Malignancies, Carcinoma Is The Type During Which Salivary Examination Shows The Large Benefits Because Of Its Direct Interaction With The Cancer Cells. Saliva Becomes The Prime Choice For Screening And Identification Of Biomarkers Because Of The Fallen Cancer Cells In The Oral Cavity ^[26].

For The Identification And Measurement Of Salivary Biomarkers, Salivary Tools Also Are Essential. Therefore, State-Of-The-Art Genomic, Proteomic, Metabolomic, Transcriptomic Approach For The Invention Of Potential Salivary Biomarkers For Oral Cancers Has Been Discussed. Through These Approaches, Biomarkers Indicate The Physiological And Pathological Conditions For The Detection And Knowledge Of OSCC At Any Stage. Therefore, Biomarkers For Cancer Identification Are Classified In Keeping With Their Distribution Of Identification Specificity. Cancer Biomarkers Can Be Classified (Table 1) On The Basis Of Disease State, Biomolecules, And On Other Criteria

Table 1; CLASSIFICATION OF ORAL CANCER BIOMARKERS

<p>BASED ON BIOMOLECULES</p>	<ul style="list-style-type: none"> • DNA BIOMARKERS • PROTEIN BIOMARKERS • RNA BIOMARKERS • GLYCO BIOMARKES
<p>BASED ON DISEASE STATE</p>	<ul style="list-style-type: none"> • PREDICTION BIOMARKERS • DETECTION BIOMARKERS • DIAGNOSIS BIOMARKERS • PROGNOSIS BIOMARKERS
<p>BASED ON OTHER CRITERIA</p>	<ul style="list-style-type: none"> • PATHOLOGICAL BIOMARKERS • IMAGING BIOMARKERS • IN SILICO BIOMARKERS

Among All Malignancies, OSCC Shows The Best Benefits From Salivary Examination. The Most Significant Reason For The Diagnostic Role Of Saliva Is That The Cancerous Cells Shed Directly Into The Mouth Hence Making It The Primary Choice For Identification Of Biomarkers For OSCC ^[28].

Salivary Tools For The Measurement And Investigation Of Alterations In Particular Salivary Molecules Such As Proteins, Genes, Enzymes, Cytokines, Metalloproteinases, Cytokeratin, Growth Factors, Etc., In OSCC Are Summarized In Table 2.

Table 2; Protein Biomarkers Identified In Unstimulated Whole Saliva (Usws) For The Detection Of Oral Squamous Cell Carcinoma (Osc) Detection.

Candidate Biomarkers	Techniques	Clinical Significance	References
Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin 1a (IL-1a), Interleukin 1b (IL-1b), TNF-A, Tissue Polypeptide Antigen (TPA), Cyfra 21-1, Cancer Antigen 125 (CA 125), Telomerase, Mac-2 Binding Protein (M2BP)	ELISA	These Cytokines Are Proinflammatory And Proangiogenic In Nature, Found To Be Indicators Of Carcinogenic Transformation From Oral Precancerous Lesions To Oral Cancer. Cyfra 21-1, CA 125, And TPA Markers Are Used As A Diagnostic Tool, Telomerase Activity Is Seen In Tumor Cells And Is Responsible For Maintenance Of Telomere Length Throughout Chromosome Replication. M2BP Helps In Detection Of OSCC.	[29], [30], [31], [32], [33], [34], [35], [37]
CD44, CD59, Profilin, MRP14	Immunoblot	CD44 And CD59 Differentiate Cancer Frombenign Diseases With Very High Sensitivityand Specificity, Whereas MRP14 Is Acalcium-Binding Protein With Sensitivity Of90% And A Specificity Of 83% In Cancer Detection.	[36], [37]

2. CONCLUSION:

Salivary Diagnostics Is A Dynamic And Emerging Field Utilizing Molecular Diagnostics To Aid In The Diagnosis Of Oral And Systemic Diseases And Using The Salivary Biomarkers For Disease Detection.Saliva Is A Bio Fluidrich In Diagnostic Indicators For Both Oral And Systemic Disorders. It Is A Non-Invasive, Uncomplicated, Diagnostic Tool. Discovering And Understanding Saliva-Based Biomarkers Could Have A Considerable Role In Establishing Oral Fluids As A Credible Diagnostic Bio Fluid. As Detailed Above, Unique Saliva-Based Biomarkers Can Be Correlated To Certain Diseases And May Provide Critical Information Regarding An Individual's Current Physiologic State.

Salivary Biomarkers Is Useful In The Diagnosis Of Variety Of Diseases. More Studies On Salivary Biomarkers May Prove Greater Insight In To Various Systemic Diseases In Human Population.

Ethical Clearance – Not Required Since It Is A Review Article

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