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Review Article

RE-DESIGNED, RE-ENGINEERED AND RE-INVENTED: THE CURIOUS LIFE OF THE BIOMARKER

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ABSTRACT

Early detection of any diseases plays a important role in successful treatment. Early diagnosis and treatment reduces the severity and possible complications of the disease activity. Medical researchers are devoted to finding molecular disease biomarkers that reveal a hidden risk, before the disease becomes complicated. Saliva and other body fluids, containing a highly complex mixture of substances, rapidly gaining popularity as a diagnostic tool. Periodontal disease is a multifacorial disease of the oral cavity comprising a group of inflammatory conditions affecting the supporting structures of the dentition. Saliva and other body fluids like GCF as a mirror of oral and systemic health, is a valuable source for clinically relevant information because it contains biomarkers specific for periodontal diseases. This review highlights the various potentials of saliva as a diagnostic biomarker for periodontal diseases.

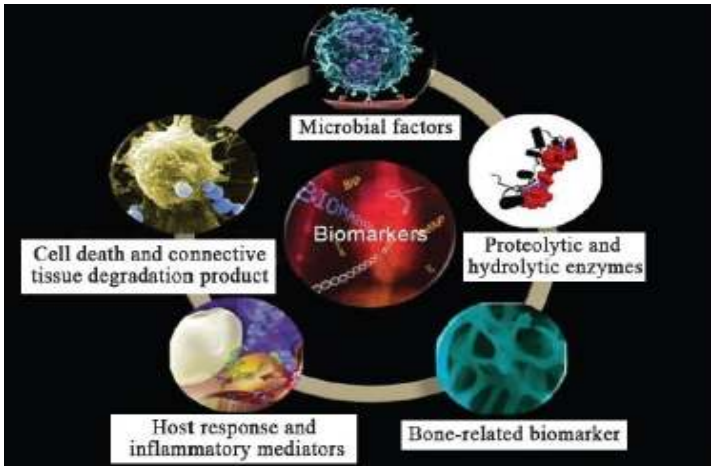
Keywords: Biomarker, Periodontal diseases, Saliva, body fluids.

INTRODUCTION

In medicine, a biomarker is a measurable characteristic that reflects the severity or presence of some disease state[1]. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism.

A biomarker can be a substance that is introduced into an organism as a means to examine organ function or other aspects of health. For example, rubidium chloride is used as a radioactive isotope to evaluate perfusion of heart muscle. It can also be a substance whose detection indicates a particular disease state, for example, the presence of an antibody may indicate an infection. More specifically, a biomarker indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue[2]. They may indicate either normal or diseased processes in the body.biomarkers can be specific cells, molecules, or genes, gene products, enzymes, or hormones. Complex organ functions or general characteristic changes in biological structures can also serve as biomarkers. Although the term biomarker is relatively new, biomarkers have been used in pre-clinical research and clinical diagnosis for a considerable time. For example, body temperature is a well-known biomarker for fever. Blood pressure is used to determine the risk of stroke. It is also widely known that cholesterol values are a biomarker and risk indicator for coronary and vascular disease, and that c-reactive protein (CRP) is a marker for inflammation[3].

In molecular terms biomarker is "the subset of markers that might be discovered using genomics, proteomics technologies or imaging technologies. Biomarkers play major roles in medicinal biology. Biomarkers help in early diagnosis, disease prevention, drug target identification, drug response etc.

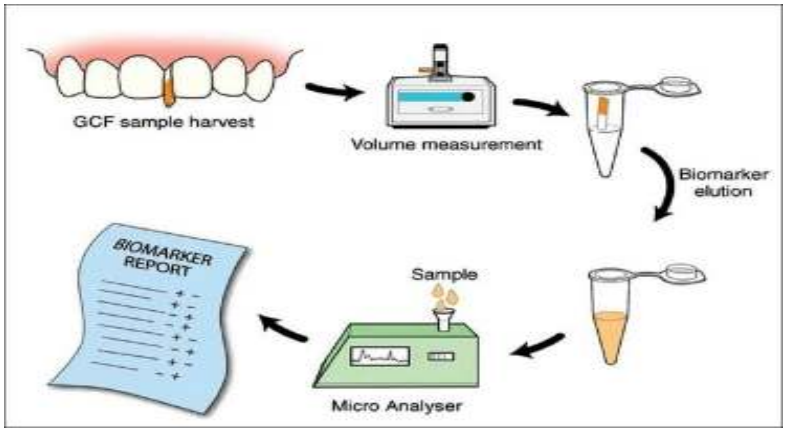


Diagnostic Biomarkers for Oral and Periodontal Diseases

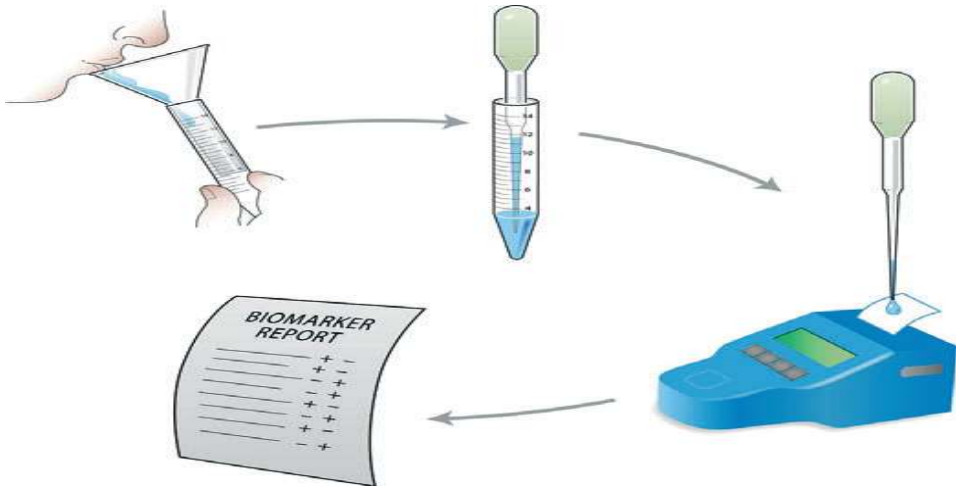
Periodontitis is a group of inflammatory diseases that affect the connective tissue attachment and supporting bone around the teeth. It is widely accepted that the initiation and the progression of periodontitis are dependent on the presence of virulent microorganisms capable of causing disease. Although the bacteria are initiating agents in periodontitis, the host response to the pathogenic infection is critical to disease progression[4].

After its initiation, the disease progresses with the loss of collagen fibers and attachment to the cemental surface, apical migration of the junctional epithelium, formation of deepened periodontal pockets, and resorption of alveolar bone[5]. If left untreated, the disease continues with progressive bone destruction, leading to tooth mobility and subsequent tooth loss. A goal of periodontal diagnostic procedures is to provide useful information to the clinician regarding the present periodontal disease type, location, and severity[6]. Traditional periodontal diagnostic parameters used clinically include probing depths, bleeding on probing, clinical attachment levels, plaque index, and radiographs assessing alveolar bone level. The strengths of these traditional tools are their ease of use, their cost-effectiveness, and that they are relatively noninvasive. Traditional diagnostic procedures are inherently limited, in that only disease history, not current disease status, can be assessed. Clinical attachment loss readings by the periodontal probe and radiographic evaluations of alveolar bone loss measure damage from past episodes of destruction and require a 2- to 3-mm threshold change before a site can be identified as having experienced a significant anatomic event. Advances in oral and periodontal disease diagnostic research are moving toward methods whereby periodontal risk can be identified and quantified by objective measures such as biomarkers. Risk factors are considered modifiers of disease activity. In association with host susceptibility and a variety of local and systemic conditions, they influence the initiation and progression of periodontitis and successive changes on biomarkers. Biomarkers like saliva and gcf are fluids easily collected and contain locally and systemically derived markers of periodontal disease, they may offer the basis for a patient-specific biomarker assessment for periodontitis and other systemic diseases. Due to the noninvasive and simple nature of their collection, analysis of saliva and gcf may be especially beneficial in the determination of current periodontal status and a means of monitoring response to treatment.

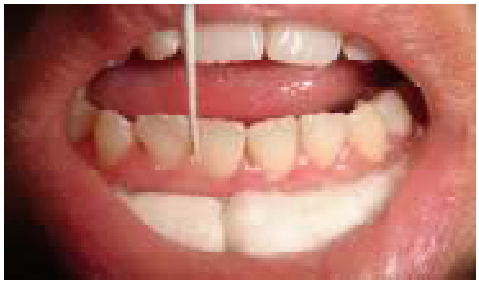
Recent advances are leading to the development of more powerful diagnostic tools for practitioners to optimize their treatment predictability.



Futuristic chairside diagnostic test based on GCF sampling. Considering the GCF fluid as a potential analyte for the screening of multiple biomarkers, a rapid, chairside diagnostic tool (represented in the figure as a Micor Analyser) or "mini-lab"



Gingival crevicular fluid is most often collected with absorbent paper points or methylcellulose filter paper strips inserted into the crevice. Standardization is obtained with timed sampling (30 seconds).



Sampling saliva instead of blood or urine provides an effective way to detect a range of biomarkers, such as proteins, electrolytes, hormones, antibodies and DNA/RNA, that can identify or predict disease.

Advantages of using saliva as a diagnostic tool include easy access, noninvasive sample collection, better patient acceptance (most patients prefer giving saliva samples over blood or urine ones), fast results and cost-effectiveness. Compared to blood, collecting saliva provides reduced risk of infectious disease transmission. Saliva collection is simple, painless and can be completed repeatedly without patient discomfort. Not requiring special training or onsite equipment, salivary diagnostics lends itself to testing at home and dental clinics, so it can be used to reach patients with limited access to preventive care due to personal, logistical or economic reasons.

Measurement errors

Imperfect measurement of the biomarker would naturally lead to deceased validity of the relation to the disease. However, there are numerous types of measurement errors other than those errors that occur in the laboratory. Problems with the collection equipment or in the transportation of specimens to the laboratory can affect the measurement of the biomarker. Improper storage of samples or changes in storage environment can also affect measurement of biomarkers[7]. Technicians are the handlers of most specimens and so appropriate training of new personnel is essential. Finally, receipt and control errors such as in the transcription of identification numbers if done by hand can always be source of error. A well organized procedures manual outlining the details for documentation, storage monitoring of specimens and maintaining records, can alleviate many of these issues. Most laboratories and large-scale studies institute a quality assurance and quality-control program to reduce measurement errors[8].

The potential for salivary diagnostics includes:

Measuring salivary protein levels to help in the diagnosis, treatment and follow-up care of breast cancer (For example, periodic salivary tests could be prescribed for women recovering from breast cancer to ensure that their cancer remains in remission.)

Portable salivary testing for abusive drugs such as cocaine, ethanol and opiates, as well as therapeutic monitoring of drugs such as methadone and certain anticonvulsants. Monitoring responses to anxiety and depression treatment.

Chairside diagnostic testing using "lab-on-a-chip" technologies to identify oral fluid biomarkers associated with good health and oral and/or systemic diseases such as Sjogren's syndrome[9].

Self-contained saliva test kit for use at the point of care that will target markers for periodontal diseases, caries, infectious diseases, pancreatic cancer, diabetes, salivary gland diseases, renal diseases, steroids and inflammatory markers for cardiovascular and pulmonary diseases.

Determining hormone levels, including estrogen (estradiol), progesterone, testosterone and cortisol (This is especially important in the case of estradiol, an indicator of premature birth and low birth-weight babies.)

Bone-Related Biomarkers From Oral Fluids Associated With Periodontal Diseases

Osteocalcin-

Serum osteocalcin is a specific marker of bone formation when formation and resorption are uncoupled. Nakashima *et al*. reported that osteocalcin levels were also significantly correlated with pocket depth, gingival index scores, and GCF levels of ALP and prostaglandin E_2.

Critical analysis-levels in oral fluids are seen during an increased periodontal disease activity.

Calprotectin-

Kido in 1999 suggested that calprotectin plays a role in immune regulation through its ability to inhibit immunoglobulin production and, of particular interest, its role as a proinflammatory protein for neutrophil recruitment and activation.

Critical analysis-Calprotectin GCF levels in patients with periodontal disease were higher than those in healthy subjects.

Osteonectin-

Bowers 1989 suggested that osteonectin is a single-chain polypeptide that binds strongly to hydroxyapatite and other extracellular matrix proteins including collagens.

Critical analysis-Osteonectin appeared to be the more sensitive marker for detection of periodontal disease status.

Osteopontin-

Sharma reported that GCF osteopontin (OPN) concentrations increased proportionally with the progression of disease and when nonsurgical periodontal treatment was provided, GCF OPN levels were significantly reduced.

Critical analysis-OPN appears to hold great promise as a possible biomarker of periodontal disease progression.

Proteomics

Proteomics is a relatively new 'post-genomic' science with tremendous potential. In contrast to gene expression studies employing oligonucleotide chips ('transcriptomics'), proteomics directly addresses the level of gene products present in a given cell state and can further characterize protein activities, interactions and subcellular distributions[10]. Proteomics has been successfully applied to areas as diverse as determining the protein composition of organelles, systematic elucidation of protein-protein interactions and the largescale mapping of protein phosphorylation in response to a stimulus[11].

Characterization of periodontal ligament (PDL) fibroblast proteome is an important tool for understanding PDL physiology and regulation and for identifying disease-related protein markers.

A total of 117 proteins have been identified from PDL fibroblasts which can serve as a reference map for future as basic research[13].

Proteomics And Periodontal Pathogens

The oral environment contains diverse micro-organisms including bacteria, fungi, protozoa and viruses. Studies of oral ecology have led to an appreciation of the complexity of the interactions that oral micro-organisms have with the host in both health and disease. Proteomics offers a new approach to the understanding of holistic changes occurring as oral micro-organisms adapt to environmental changes within their habitats in the mouth[12].

Proteomics And Tissue Engineering

Tissue engineering has evolved in recent year in effective tool for treating various pathological conditions. This technology mainly includes stem cell procurement, storage, differentiation and transplantation which is done by using specific biomarkers[13].

The use of proteomics and gene expression will advance the diagnosis and treatment of various oral pathological conditions. Advances in tissue engineering, drug delivery, gene therapy and biopharmaceuticals will present new therapeutic opportunities[14]. However, its application into the field of dentistry depends on how best oral health care practitioners will incorporate this into their practice as it requires a thorough knowledge of human genetics and application of new diagnostic and therapeutic technologies. [15]

CONCLUSION

Saliva, contains an abundance of protein and biomarkers that reflects physiological status; however, salivary diagnostics are easy, inexpensive, safe, and non invasive approach for disease detection, and possess a high potential to revolutionize the next generation of diagnostics. Although in future , the use of saliva oral fluid diagnostics appear promising for future application to diagnose periodontal diseases and to prognosticate periodontal treatment outcomes.

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