SALIVARY BIOMARKERS AS A DIAGNOSTIC INDICATOR OF PERIODONTAL DISEASE - A REVIEW

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ABSTRACT

A biomarker is a naturally occurring molecule or a gene by which a particular pathological or physiological processes, diseases, etc can be identified. Genetically a biomarker is "anything that can be used as an indicator of a particular disease state or some other physiological state of an organism". Periodontitis is a multifactorial disease of the periodontium where the host releases a series of inflammatory mediators .Saliva is being used as a diagnostic fluid for analysis of periodontal disease as it is easy, rapid and non- invasive to collect , and readily abundant. This review deals with the various salivary biomarkers of periodontal disease and the diagnostic aids available for their detection.

KEYWORDS :Periodontitis, saliva, biomarker, diagnostic aids.

INTRODUCTION

Periodontitis is a chronic inflammatory disease characterized by destruction of periodontal ligament and alveolar bone around the teeth in conjunction with the formation of periodontal pockets. The severity of periodontal disease is dependent on a dynamic equilibrium of

interactions between the microbial challenge and host immune- inflammatory responses.[1] The sub gingival micro flora trigger host defense responses as evidenced by the release of chemotactic factors, antigens, endotoxins, toxins and other products. There is a biochemical signaling in the involved tissues which has been detected in the whole saliva of patients having periodontal disease, thus making them biomarkers of the disease.[2]

Periodontitis is initiated by specific bacteria, predominantly gram negative- anaerobes, which activate tissue mechanisms that produce a series of inflammatory and immunologic changes leading to destruction of connective tissue and bone.[3]

The etiology of periodontal disease is complex, and variance in the human host response to microbial plaque relates to the host's innate, inflammatory, or immune defense system.[4]

Bacterial biofilm initiate and advance the pathogenesis of the disease. Components of microbial plaque, particularly lipopolysaccharide and other soluble products stimulate monocytes, lymphocytes, macrophages and neutrophils. The host response to periodontal pathogenic bacteria involves a complex of events that involves both local and systemic release of wide range of pro-inflammatory components such as IL1,TNFα and Prostaglandin E2, that initiates and controls inflammatory reactions[5] During the inflammatory process inflammatory products are released that migrate toward the gingival sulcus or periodontal pocket. Early diagnosis and treatment of periodontitis is important due to the destructive nature of the disease Kianane 2000[.6] These mediators of disease activity have been identified from the biological fluid saliva.[7]

SALIVA AS A DIAGNOSTIC TOOL
The diagnosis of active phase of periodontal disease and the identification of patients at risk for acute diseases is a challenge. The goal of periodontal diagnostic procedure is to provide useful information to the clinician regarding the current state of periodontal disease, type, location and severity .These findings serve as a basis for treatment planning and disease monitoring phase of treatment.

Oral fluid/saliva, called the 'mirror of the body' is a perfect medium to be explored for health and disease surveillance. It is a relatively inexpensive, noninvasive, simple and accurate screening method. It creates an ideal opportunity to bridge the state of the art saliva based biosensors and disease discriminatory salivary biomarkers in diagnostic applications. Saliva

is a fluid that is readily available and contains locally produced microbial and host response mediators, as well as systemic (serum) markers that may prove to be an aid in the diagnosis of periodontal disease.[2]

Periodontal disease initiates with inflammation of the gingival apparatus and periodontal tissues in response to bacterial plaque accumulation. The constant presence of multispecies bacterial biofilm leads to chronic inflammation and an abundance of inflammatory molecules in oral fluids.[8]

Although saliva contains diverse components with diagnostic properties, its low concentration compared with levels in the blood may prevent salivary diagnostics from being clinically practical.[9] Empowered with new and highly sensitive technologies, the lower level of analyses is no longer a limitation.

Various mediators of chronic inflammation and tissue destruction have been detected in whole saliva of patient with oral diseases. For diagnostic purpose salivary biomarkers proved more useful than serum analysis.

To date, several studies have detected one or more inflammatory markers at higher concentrations in patients who have periodontal disease compared with healthy controls.

Oral fluid biomarkers that have been studied for periodontal diagnosis include proteins of host origin (eg. enzymes and immunoglobulin's), phenotype markers, host cells (eg.PMNs), hormones, bacteria and bacterial products, ions and volatile compounds.[7]

BIOMARKERS

Biomarkers may be defined as a substance that is measured objectively and evaluated as an indicator of normal biologic processes and pharmacological responses to a therapeutic intervention.[10]

WHO defines biomarker as any substance, structure, a process that can be measured in the body or its products and influence or predict the incidence of outcome or disease.

Biomarkers, whether produced by normal healthy individuals or by individuals affected by specific systemic disease, are "Tell - Tale" molecules that could be used to monitor the health status, disease onset, treatment response and outcome. Biomarkers have now become paradigm for periodontal diagnosis, which helps in managing periodontitis patients.

NEED FOR EARLY DETECTION OF PERIODONTALDISEASE

If periodontal diseases are detected early, treatment can be easier and less painful for the patient. Left untreated periodontal disease may lead to systemic problems such as cardiovascular disease and diabetes to name a few. Therefore early screening for periodontal disease is essential during dental examination. Significant advances are in development for screening of periodontal disease

SALIVARY BIOMARKERS OF PERIODONTAL DISEASE

Salivary biomarkers are classified as

1. Proteomic biomarkers

2. Genetic/genomic biomarkers

3. Microbial biomarkers

PROTEOMIC BIOMARKERS OF PERIODONTAL DISEASE

Specific salivary proteomic biomarkers have been identified for three key features of the pathogenic process in periodontal disease- inflammation, collagen degradation and bone turnover.

Innate host defense responses are triggered by bacterial lipopolysaccharide and other microbial components. This recruits polymorph nuclear neutrophils (PMNs), monocytes and activated macrophages to the inflamed site which releases numerous cytokines such as prostaglandin E2, TNF α and interleukins IL-1 and IL-6. As a consequence matrix metalloproteinase (MMPs) which are powerful collagen destroying enzymes are produced by the alveolar bone and (PMNs).

Combined elevated salivary levels of MMP-8 and IL-1β increased the risk of developing periodontal disease by 45 fold, and elevations in all three biomarkers correlated with individual clinical parameters that are indicative of periodontal disease.[11]

Saliva contains biomarkers specific for unique physiological aspects of periodontitis and qualitative changes in the composition of these biomarkers could be diagnostic. The increase in salivary alkaline phosphatase activity in periodontitis could be associated with alveolar bone loss.[12]

GENETIC/GENOMIC BIOMARKERS OF PERIODONTAL DISEASE

Reports of genetic polymorphisms associated periodontal disease are increasing and strong evidence supports the proposal that genes play a role in the predisposition and progression of periodontal disease.[13] A number of studies examined the link between polymorphisms within the host factors that included the gene encoding inflammatory cytokines such as IL-1 and TNF α.[14]

Levels of 8- hydroxy- deoxyguanosine, a product of oxidative DNA damage was found to be significantly increased in the saliva of patients with periodontitis and its reduction after periodontal therapy[15] making it an informative biomarker for evaluating periodontal status and the efficacy of periodontal treatment.

MICROBIAL BIOMARKERS OF PERIODONTAL DISEASE

Saliva is regarded as a microbial reservoir and serves as a carrier of bacterial transmission.[16] Aggregatebacter actinomycetemcomitans, Porphyromonos gingivalis, Tannerala forsyths, Fusobacterium nucleatum, Prevotella intermedia, Treponema denticola are some of the microbial organisms of periodontal disease. A micro assay system was designed that allows rapid screening of complex microbial communities and will contribute to the search of microbial biomarkers of periodontal disease.

Fig: 1 showing various biomarkers present in saliva.

DEVICES FOR MEASURING SALIVARY BIOMARKERS OF PERIODONTAL DISEASE

NANO- BIOCHIP TECHNOLOGY

It is a "lab-on-a-chip" platform that uses oral fluids in rapid tests to accelerate clinical decision making.[17] It uses a miniaturized sensor. This sensor system is based on a bio-micro-electromechanical system platform. The Nano chip processes fluids so as to provide a digital fingerprint that can be correlated with local chemical environment, detecting PH, electrolytes, bacterial toxins and proteins. The POC collection device collects saliva (100-300μl) and delivers into the nano-biochip. A network of fluidic components ensures the complex transfer and process of saliva samples to the multiplex bead array to provide quantitative information of target biomarkers of disease. This provides a determination of a patient's periodontal disease-risk profile, current disease activity and response to therapeutic intervention.[18]

RAPID PERIODONTAL TEST

The saliva of periodontitis patients is collected using this kit which employs a filter paper strip which is sent for analysis. This method is advantageous because the contributing inflammatory mediators and tissue destructive molecules associated with periodontitis are found in saliva.

MY PERIO PATH

It is a DNA based salivary test kit. It identifies the type and concentration of specific periodontal pathogenic bacteria that are known to cause periodontal disease thus enabling the clinician with better risk assessment.

MYPERIO ID

It is also a salivary based diagnostic kit. It identifies individual genetic susceptibility to periodontal disease and enables the clinician to establish which patients are at increased risk for severe periodontal infections due to an exaggerated immune response.

ELECTRONIC TASTE CHIPS

Several studies have reported elevated serum CRP levels in periodontitis patients. Salivary CRP may represent a novel approach for diagnosing and monitoring chronic inflammatory diseases including CVD and periodontal diseases. Electronic Taste Chip is a lab-on-a chip system for measuring CRP analyses in saliva. With this technique it was possible to

quantitate the difference in CRP levels between healthy individuals and patients with periodontal disease.[19] The prospect of a commercially available ETC lab-on-a-chip platform that can detect multiple biomarkers for early diagnosis of periodontal disease is promising.

CONCLUSION

It is likely that the development of saliva based biomarkers will impact and expand the role of dentists. Integrating the new salivary diagnostic methods into clinical practice is important to aid dental professionals in making essential health related decisions for patients. In the near future, taking a salivary sampling in a dental clinic will become a routine procedure.

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