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Original Research Paper

Periodontology

BIOMARKERS IN PERIODONTICS – A REVIEW

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ABSTRACT Acute periodontitis is known as the 6th most common disease affecting more than 740 million people worldwide. The diagnosis of periodontal disease is highly dependent on the examination of normal clinical parameters. However, they symbolize the past, rather than the present, or the progression of the disease and the clinical condition, the potential consequence of periodontal treatment. In some cases periodontal disease and critical biomarkers have been extensively tested to address these problems and other biomarkers have been interpreted as point-of-care (PoC) tests. The main purpose of this review article is to provide an overview of the various biomarkers in diagnosing and controlling periodontal diseases. Among the improved PoC tests to date, the active matrix metalloproteinase-8 showed promising results regarding diagnostic and predictive values. On the other hand, further research is needed to increase sensitivity and clarity by combining more than one biomarker with the integration of these test kits with periodontal risk assessments. In addition, the suitability of these test kits requires that they be investigated using the results of other independent studies and the impact of these testing tools, as well as the effects of risk factors for periodontal diseases, such as smoking and diabetes, and needs will be tested.

KEYWORDS : diagnostic; periodontal diseases; prognostic; biomarkers; point-of-care test; MMP8.

INTRODUCTION

Periodontitis is a group of inflammatory diseases that affect the attachment of connective tissue and supporting bone around the teeth where its onset and progression depends on the emergence of harmful microorganisms that can cause disease.[1] Activation and mediation of inflammatory responses that ultimately be responsible for the harmful events that occur in the periodontium. Studies of the immune response to pathogenic bacteria have contributed to the recent understanding of the pathogenesis of periodontal diseases.[2]

A biomarker or biological marker is an appropriate measure and evaluated as an indicator of a common biologic process, pathogenic process or pharmacologic response to a medical intervention.[3]

A complete diagnostic mark should indicate the presence of a disease process before major clinical damage occurs. Biomarkers should have high precision and sensitivity, and one should be easy to use on the side of the chair or as a tool for home use or testing. Based on our current understanding of the complexity of periodontitis, the recognition of a single diagnostic biomarker for all types of periodontitis seems absurd. However, researchers have been actively seeking clear signs of periodontitis in the gingival crevicular fluid to perform a simple test, which will be used on the side of the chair, to determine if a patient is suffering from periodontitis and needs treatment, as opposed to another patient who does not need intervention although with gingivitis.[4]

4 clusters of markers released during the immune response may be appropriate as biomarkers for periodontitis. These are (1) host-derived enzymes; (2) tissue breakdown products; (3) host response modifiers; (4) Cytokines.[5]

Criteria for the ideal biomarker

The biomarker selectively should be flexible, safe to use, easily measured, affordable, and can be collected without attack.[6] In addition, the biomarker should be very sensitive to accurately identify those (infected) and accurately. beware of those who do not have the disease (truth-negative) .[7] These diagnostic methods increase the effectiveness of biomarker as a tool for predicting and diagnosing and effectively demonstrating patients' responses to treatment. In addition, consistency of results for all races, ages, and genders is an important factor in a good biomarker.

Various Sources of Biomarkers of Periodontal Disease in the Oral Cavity

Saliva, Gingival crevicular fluid (GCF), Peri-implant sulcular fluid (PISF), and mouthwash are always reliable sources of organic matter in the oral cavity. This fluid may be collected in an unusual way, with the potential for indicating periodontal health and disease status by examining the biomarkers within it.[8]

Advantages of traditional diagnostic methods:

- Easy to use,
- Cost effective,
- It is not invasive,
- Measure the severity of the disease.[9]

Limitations of traditional periodontal diagnostic techniques

1. Clinical and radiological estimates of attachment loss are inaccurate
2. Full oral recording is necessary due to the specific background of the progression of periodontal disease.
3. The individual risk factor for periodontitis varies both genetically and over time
4. All clinical diagnostic methods provide information about past disease function and cannot diagnose current disease function.[10]

Demand for biomarker under diagnosis periodontal treatment leads to failure of periodontal treatment. In that

case the researchers produced biological signs that indicated the presence or absence of periodontal disease.[11] The biological sources selected included saliva, serum, and crevicular gingival fluid.

Sources of biomarkers:

Salivary biomarkers specific to periodontal disease

In periodontal disease, bacterial products initiate an immune response and, from this, activate polymorphonuclear neutrophils, momocyte and macrophages, by the involvement of these cells on site and the release of cytokines such as prostaglandins (PGE2), Tumor necrosis factor (TNF), as well as interleukins (IL-1 and IL-6), which lead to the level of the inflammatory process.

As a result they produce matrix metalloproteinases (MMPs) which are collagen enzymes that destroy.[12]

Classification of various salivary biomarkers (Giannobile et al 2009) Major salivary gland secretion mediators associated with periodontal diseases:

Marker	Relationship with periodontal disease	Type of periodontal disease
Specific		
Immunoglobulins (IgA, IgM, IgG)	Interfere in adherence and bacterial metabolism /increased concentration in saliva of periodontal patients	Chronic and aggressive
Nonspecific		
Mucins	Interfere with the colonization of Aggregatibacter actinomycetemcomitans	Aggressive
Lysozyme	Regulates biofilm accumulation	Chronic
Lactoferrin	Inhibits microbial growth/ increased correlation with *A. actinomycetemcomitans*	Aggressive
Histatin	Neutralizes lipopolysaccharide and enzymes known to affect the periodontium	Chronic and aggressive
Peroxidase	Interferes with biofilm accumulation/increased correlation with periodontal patients	Chronic
Systemic		
C-reactive protein	Increased concentration found in serum and saliva of periodontal patients	Chronic and aggressive

GCF Biomarkers Specific to Periodontal Disease

Gingival Crevicular Fluid is based on serum and locally produced methods such as tissue fragmentation products and sub-extracts of subgingival biofilm. A variety of substances found in the Gingival Crevicular Fluid include inflammatory mediators, cytokines, leukocytes, enzymes, living ions, tissue degradation products and proteins. These machine parts provide insight into the healing power of the periodontium. In contrast, it also shows about the evolutionary mechanism of the survival of certain bacteria within the gingival crevice and in the gut.12 Symptoms of various biological diseases such as interleukins (IL-Iα-IL-1β) Tumor necrosis factor alpha TNF α, enzymes such as acid phosphatase, alkaline phosphatase, matrix metallop roteinase, collagenase, elastase are widely used in periodontal studies to evaluate the resolution of periodontal disease.13 Along with this it also constitutes organic and inorganic ions (Figure 1).

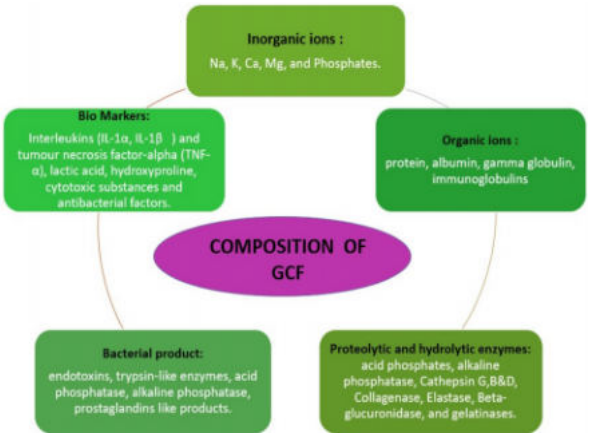

Figure: 1 Description of gingival crevicular fluid composition.[14]

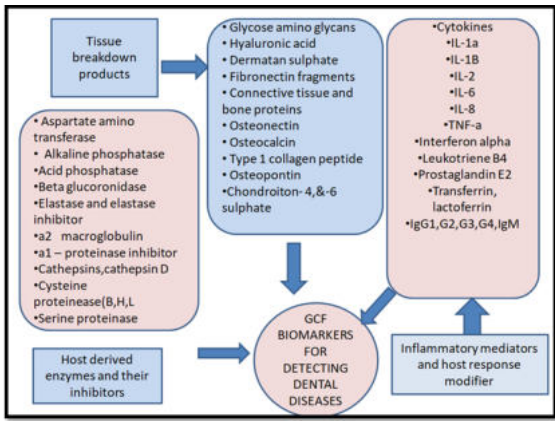

Figure: 2 GCF biomarkers for detecting dental diseases[15,16]

Blood Components

Blood Serum is a matrix commonly used in biological and clinical studies. Many authors urge to use the appropriate matrix. Both plasma and serum are found throughout the blood that undergoes various biochemical processes after bleeding. Serum from the blood is obtained when the blood is thickened. Blood can be a widespread manifestation of a condition or phenotype. Its cellular components include erythrocyte, thrombocytes, and lymphocytes. A portion of a blood component is called plasma, in which all blood components are stored. The concentration of various plasma components is always determined in clinical practice. In this approach, it is not surprising that biomarkers are required in plasma.[17]

Subgingival Plaque

A number of certain periodontal diseases have been implicated in periodontal disease, including *Tanerella forsythensis, Porphyromonas gingivalis and Treponema denticola*. In periodontal disease *Aggregatibacter actinomycetemcomitans* have been linked to premature onset of periodontal disease and aggressive periodontitis, while complex red bacteria are associated with chronic periodontitis.

Principles for the use of microbial analysis to monitor periodontitis:

1. Diagnosis of certain periodontal diseases,
2. Identify the tendency of antibiotics to infect living organisms in infected areas,
3. Predict the function of diseases.[18]

Expired air

Volatile sulfur compounds (VSC's), particularly hydrogen sulfide and methylmercaptan, have been linked to halitosis.

Swelling of the saliva has been recognized as a diagnostic sign that may contribute to periodontal disease. For example, pyridine and Pico lines are only available in patients with moderate to severe periodontitis. In addition, saliva is considered a useful means of checking oral odor.[19]

Diagnostic kits

To diagnose the periodontal diseases, the perfect diagnostic test must be:

1. Quantitative
2. Highly sensitive method capable of analyzing a single periodontal site in health as well as disease
3. Reproducible
4. Highly specific
5. Simple to perform
6. A rapid, one or two stage procedure
7. Noninvasive
8. Versatile in terms of sample handling, storage and transport
9. Amendable to chair-side use
10. Economical
11. Dependent on simple and robust instrumentation.[20]

They are categorized as microbiologic kits, biochemical kits, and genetic kits [Table 1]. Mani et al.

Classification	Trade name	Evaluation
Microbiological	Evalusite (Eastman Kodak Company)	Visual detection and differentiation of antigens from *Aa*, *Pg* and *Pi*
	Perioscan	Detects periodontal pathogens *B. forsythus, Pg, T. denticola* as well as certain *Capnocytophaga* species that produce trypsin like enzyme
	Omnigene (DMDx)	DNA probe for detection of *Aa, Pg*
	IAI Pado Test	Oligonucleotide probe for detection of *Aa, Pg, T. forsythia* and *T. denticola*
Biochemical	Perio-Check	Detects neutral proteases like collagenases in GCF
	Prognos-Stik	Detects serine proteinase elastase in GCF Detects AST in GCF
	PocketWatch	Detects AST in GCF
	PerioGard	Detects VSC
	Perio 2000	Detects bacterial toxins and proteins Detects MMP-8 in GCF
	TOPAS	Saliva-based detection of MMP-8
	Dip Stick	Saliva-based detection of IL-1, IL-8 Detects CRP
	IMPOD	
	OFNASET	
	ETC	
Genetic	PST	Detects IL-1 polymorphism
	MyPerioID	Saliva-based detection of genetic susceptibility

Aa: Aggregatibacter actinomycetemcomitans, Pg: Porphyromonas gingivalis, Pi: Prevotella intermedia, B. forsythus: Bacteroides forsythus, T. denticola: Treponema denticola, T. forsythia: Tannerella forsythia, GCF: Gingival crevicular fluid, AST: Aspartate aminotransferase, VSC: Volatile sulfide compound, MMP: Matrix metalloproteinase, IL: Interleukin, CRP: C-reactive protein, TOPAS: Toxicity prescreening assay, IMPOD: Integrated microfluidic platform for oral diagnostics, OFNASET: Oral Fluid NanoSensor Test, ETC: Electronic taste chip, PST: Periodontitis susceptibility trait test.

DISCUSSION

Due to a variety of diagnostic methods, the International Consortium for Biomarkers of Periodontitis community has already been sought in 2015 but has not yet been established.[21] The salivary biomarker symptoms of periodontitis still appear to be consistent with routine clinical trials.[22]

Most existing studies are unable to perform quality meta-analysis procedures, and as a result, their results are not considered in the global search for a reliable PoC diagnostic tool for periodontitis. However, great strides have been made in developing sensitive and precise saliva diagnostic services such as blood or urine testing.[23] A combination of biological symptoms and saliva during periodontopathic bacteria can also be used to assess the risk of periodontitis and is therefore easily used by many people. surveys.[24]The most recent meta-analysis revealed that many promising biomarkers could not be considered for lack of convincing studies of those with significant differences between groups.[25] It was concluded that future studies should be based on recent methodological agreements.[26] Standard clinical agreements, research, and focuses on explicitly biased controls .[26]Prospect studies should guide previous approaches, prefer saliva collection that can be encouraged in many research groups, and incorporate confusing features. In peri- implantitis, the current heterogeneity of subjects precludes direct testing of the salivary markers, and randomized clinical trials are required.[27]Saliva is readily available to make the collection process fairly straightforward, however when more samples are needed. Its collection is non-invasive, which makes the procedure more satisfying for patients and favors a stress-free appointment. Many risks associated with blood transfusions do not apply to saliva. There is no potential for infection among patients if used improperly and poses a risk to health workers. Due to low levels of antigen in the saliva, HIV, and hepatitis B infections are much lower in the risk of saliva than

blood.[28] Saliva is also easier to treat because it does not block it like blood. As saliva tests become more common, the cost may be lower than what is currently available for urine / blood samples. Although,due to the variability of the strategy, today's analysis is still very expensive.

Gingival crevicular fluid has a number of diagnostic benefits, such as mediators that contribute to inflammation and periodontitis-destroying tissue molecules that appear, and can be detected, in GCF. However, GCF analysis is time consuming, requiring multiple samples from individual dental sites. This process requires a lot of labor and to some extent requires expertise, requires equipment to measure and measure water volume. In conclusion, investigations are expensive, require laboratory-based testing and often cannot be done near the chair. In addition, GCF analysis involves small amounts of fluid, usually about 1 □L, which contributes to laboratory analysis, and can be easily contaminated with blood, saliva, or plaque. [29] Testing seems promising for the future. New technologies such as lab-on-a-chip and microfluidic equipment have the ability to control complex oral fluids, such as saliva and GCF, and provide a determination of the patient's risk profile for periodontal disease, current disease function, and response to treatment interventions. This approach should accelerate clinical decisions and monitor the development of episodic disease in chronic infectious diseases such as periodontitis.[30]

CONCLUSION

From various measurements such as periodontal testing to complex genetic analysis and cell testing to detect biomarkers at different stages of the disease, great progress has been made in understanding the therapists involved in the onset and progression of periodontitis. Seat-based diagnostic aids provide a quick, repetitive diagnostic method and the results can be used to motivate the patient. They are particularly useful in creating an active environment and monitoring patients after treatment to assess response to treatment and recurrence of diseases. The integration of new saliva diagnostic techniques into medical practice is essential to assist dentists in making decisions related to the health of patients. The success of any treatment in periodontology is based on the accuracy of the early diagnosis. At present, most chronic periodontal diseases can be adequately treated using an existing diagnostic method, although it is always exciting to be able to diagnose a "functional disease" as it happens, rather than months later.

Many biochemical chair-side diagnostic kits have been sold. The chairman's recent separate commercial examination on the catch marks and viruses of periodontal disease offers prospects that can make local monitoring possible. However, the physician should ensure that the use of these tests will benefit the patients themselves in terms of both the amount of diagnostic information received and the cost of money and time. These current advances are leading to the development of highly diagnostic tools for physicians to strengthen the certainty of their treatment. The future is bright for the use of a quick, easy-to-use diagnostic test that will provide a comprehensive patient evaluation that can guide and transform modified dentistry treatments, leading to individual, orally targeted oral health care.

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