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Host Derived Biomarkers in Periodontitis: an Insight

Dr. Varun Dahiya[1]*, Dr. Pradeep Shukla[1], Dr. Artika Sharma[1], Dr. Shagun Gulia[2]

[1]Department of Periodontology & Implantology, D. J. College of Dental Sciences and Research, Modinagar, India

[2]Department of Prosthodontics, SGT Dental College and Hospital, Gurgaon, India

Review Article

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***For Correspondence**

Dr. Varun Dahiya Professor
Department of Periodontology and ImplantologyD.J.college of Dental Sciences and Research Modinagar, India,
Tel: 09810560139

E-mail: dr.varundahiya@gmail.com

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ABSTRACT

A major challenge in clinical periodontics is to find a diagnostic method that could predict the active phase of the disease, severity of the disease as well as treatment outcome of the disease. To meet this challenge, the study of various Biomarkers of soft tissue and bone destruction has gained popularity. But still it is difficult to find a reliable biomarker of periodontal tissue destruction with high sensitivity, specificity and utility.

INTRODUCTION

Periodontitis is defined as an inflammatory disease of the supporting structures of the teeth caused by specific micro-organisms or group of specific micro-organism resulting in progressive destruction of PDL and alveolar bone with pocket formation, recession or both. It is one of the most common oral diseases and is characterized by gingival inflammation and alveolar bone resorption [1]. According to a report by the World Health Organization, severe periodontitis leading to tooth loss was found in 5–15% of most populations worldwide [2]. So, early diagnosis of periodontal disease is mandatory. Traditional diagnostic procedures, that include the routine clinical measures like PD, CAL and various indices like PI, GI, BOP etc. are inherently limited, in that only disease history, not current disease status, can be assessed. These diagnostic methods are not precisely accurate and only allow retrospective diagnosis of attachment loss.

Therefore, an ideal periodontal diagnostic procedure should be designed which would be able to:

1. Screen the susceptible individuals for periodontitis from the population.

2. Differentiate the active and inactive sites.

3. Predict future tissue destruction in particular site or individual.

4. Monitor the response to periodontal therapy.

Given the complex nature of periodontitis, it is unlikely that one single clinical or laboratory examination can address all issues concerning diagnosis, classification, and prognosis [3]. 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.

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The biomarkers for periodontal disease activity can be detected in various host derived fluids which include oral diagnostic fluids like GCF and Saliva as well as blood components like Serum and Plasma. Each of these diagnostic fluids has their own advantages and limitations.

The aim of this review is to state the various host derived diagnostic biomarkers related to soft tissue and bone degradation in periodontitis.

Biomarkers and the principle behind using them in diagnosis

A biomarker is defined as a "parameter that is objectively measured and evaluated as an indicator of normal biological or pathological processes, or pharmacological responses to a therapeutic intervention", (Biomarker Definitions Working Group). The sentinel principles for disease specific biomarkers include:

1. Should be able to detect the disease.
2. Should be able detect the stage of the disease.
3. Should be able to predict the response to treatment.
4. Should be able to determine the treatment efficacy.
5. Should monitor the treatment compliance.
6. Should monitor the progression/recurrence of the disease.

Sources of biomarkers for periodontitis

The sources of biomarkers in periodontal disease include:

1. Subgingival bacteria and their products.
2. Host inflammatory & immune products.
3. Proteolytic & Hydrolytic Enzymes.
4. Enzymes released from dead cells.
5. Connective tissue degradation products.

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GCF

Gingival crevicular fluid (GCF), a serum transudate or inflammatory exudate, can be collected from the gingival crevice surrounding the teeth. As such, the fluid reflects the constituents of serum, the cellular response in the periodontium. The study of GCF has focused on defining the pathophysiology of periodontal disease, and identification of a potential diagnostic test for active periodontitis.

The major advantage of using GCF as a diagnostic fluid is that the method of collection of GCF is non-invasive, as well as the fluid gives the site specific diagnosis of the periodontal disease.

The various limitations that are present in analyzing GCF as a diagnostic fluid are discussed in **(Table 1).**

Table 1. Limitations in analyzing Gcf sample.

The method is not accurate and non-reproducible because of small sample size
No uniform consensus on choice of collection device, its placement, site of selection and collection time
Potential depletion of sample by prolonged collection
Potential contamination by serum components and saliva
Loss of sample from the collection device
Variability in calculation of data as absolute measures or as flow rates.

SALIVA

Saliva is considered as the body's mirror and it can be used to detect the oral as well as systemic status. Whole saliva contains various constituents which include secretions from exocrine glands, GCF, and dietary and oral plaque components. Recently, the use of whole saliva as a means of evaluating host derived products as well as exogenous components has been suggested as a potential diagnostic marker for disease susceptibility [4]. The various advantages and disadvantages of using Saliva as a diagnostic fluid **(Tables 2 and 3).**

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Table 2. Advantages of using saliva as a diagnostic tool.

The collection of sample is easy and non-invasive
Saliva can be collected with devices that will be stable at room temperature for extended periods
Many of the hazards associated with blood collection such as cross - contamination among patient when used improperly and present a danger to health care personal do not apply to saliva
The presence of secretory leucocyte protease inhibitor (SLPI) may be another factor contributing to the safety of saliva as a diagnostic specimen. SLPI expresses anti-virus activity against free HIV-1 and lymphocyte derived tumour cell lines.

Table 3. Limitations of using salivary sample as a diagnostic tool.

Saliva represents a pooled sample from all periodontal sites, thereby giving an overall non-specific assessment of a particular disease or risk status at the subject level
The samples are not sterile and are subjected to bacterial degradation over time
Interpretation of saliva assays is still difficult although diurnal and monthly patterns generally parallel serum values; absolute ranges show variability in different studies
Proficiency testing programmes are not yet available for saliva, which makes validation of laboratory tests for certified laboratories difficult

BLOOD COMPONENTS

Various studies have evaluated the molecular markers of tissue destruction in serum or plasma: these manifestations of periodontal diseases are mainly sought to clarify the possible interactions between periodontitis and various systemic diseases and/conditions. Serum or plasma provides information about the inflammatory stimulus and/or response generated in circulation towards the periodontal pathogens that colonize in the subgingival area [5].

The major disadvantage of using blood components as a diagnostic fluid includes chances of cross – contamination as well as a potential risk to the health care personnel.

The various host derived soft tissue and bone degradation biomarkers in periodontics have been discussed in **(Table 4).**

Table 4. Host derived biomarkers.

Component	Type of molecule	Function	Associated with	Found as
Alkaline Phosphatase [6,7,8]	Membrane Glycoprotein	Hydrolysis of Phosphate Ester Bonds	Treatment	Host derived enzyme
Cathepsin B [9,10]	Cysteine Proteinase	Proteolysis	Severity of the disease and treatment	Host derived enzyme
Cathepsin K [11]	Cysteine Proteinase	Proteolysis	Severity of the disease and treatment	Host derived enzyme
Oncostatin M [12-14]	a member of the interleukin-6 (IL-6) family	recruiting leukocytes to inflammatory sites	Severity of the disease and treatment	Individual Bone Biomarker
Collagenase 2 (MMP-8) [15-17]	Metalloproteinase	Hydrolysis of intercellular matrix	Severity of the disease and treatment	Host derived enzyme
Gelatinase (MMP-9) [16,18]	Proteolytic Enzyme	Hydrolysis of intercellular matrix	Treatment	Host derived enzyme
Collagenase 3 (MMP-13) [19]	Metalloproteinases	Hydrolysis of intercellular matrix	Treatment	Host derived enzyme
Osteocalcin [20,21]	Bone carboxygultamic acid protein	Calcium binding	Severity of the disease	Tissue breakdown product
Pyridinoline cross links (ITCP) [22-25]	Bone specific molecule	Connective tissue metabolism	Severity of the disease and treatment	Tissue breakdown product
Osteonectin [26]	Single-chain polypeptide	Binds strongly to hydroxyapatite and other extracellular matrix proteins including collagens.	Severity of the disease	Individual Bone Biomarker
Osteopontin [27,28]	Single-chain polypeptide	Highly concentrated at sites where osteoclasts are attached to the underlying mineral surface	Severity of the disease	Individual Bone Biomarker
RANKL [29,30]	Cytokine	Promotes joint inflammation and bone destruction		Inflammatory mediator
OPG [29,30]	Glycoprotein	Decoy receptor for RANKL, inhibits osteoclast formation		Tissue breakdown product

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Aspartate amino transferase [7,8]	Lysosomal enzyme	Catalyzes transfer of amino group of aspartate to alpha-ketoglutarate		Host derived enzyme
TIMP-1 [16,17,31]	MMP Inhibitor	Inhibits MMP 1		Inflammatory mediator
Elastase [32,33]	Seriene Proteinase	Cleavage of elastin, collagen, proteoglycans		Host derived enzyme
Myloperoxidase [34]	Lysozomal oxidative enzyme	Generation of reactive oxygen species		Host derived enzyme
Dipeptidyl peptidase II or 1V [35]	Lysozomal proteinase	Peptide cleavage	Severity of the disease	Host derived enzyme
Pro-inflammatory cytokines [36-38]	Cytokines	Induce Inflammatory reaction		Inflammatory mediators

Apart from these few more biomarkers like serum cortisol levels, platelet activation factor, soluble intercellular adhesion molecules, surfactant protein D as well as serum calcium levels have been studied and have shown promising results as biomarkers of chronic periodontitis **(Table 5).**

Table 5. Other biomarkers of interest.

Component	Type of molecule	Function
Hs-CRP [39]	Acute phase reactant	Acts in innate immune response
Serum Amyloid A [40]	Acute phase protein	Associated with high density lipoprotein (HDL)

DISCUSSION

Various biomarkers have been studied but there is no evidence till date that certain type of biomarker is more sensitive or specific than the other one. Even the methods of collection of fluids for detection of biomarkers has its own benefits and risks associated. But the use of biomarkers is beneficial in early detection of the periodontal disease process and hence early treatment rendering along with evaluating the treatment outcomes.

CONCLUSION

There exists extensive evidence that molecules in the saliva, GCF and serum correlate with tissue inflammation and bone destruction. But, highly specific and sensitive biomarkers for diagnosis and monitoring of periodontal disease are still needed for early diagnosis and better detection of the disease process.

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