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BIOMARKERS- A PEEK INTO PERIODONTAL DISEASE PROGRESSION

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ABSTRACT

A biomarker is naturally occurring molecule or gene or characteristic by which a particular pathological process or a disease can be identified. Conventional periodontal disease diagnosis is based on summation of past events. It also cannot predict the future of disease progression. There is always a quest for newer diagnostic techniques which along with identifying the current status help in predicting the future progression. Periodontal biomarkers can certainly be one such candidate. There is plethora of biomarkers present in oral fluids viz. Gingival Crevicular Fluid, saliva and blood whose levels are specifically associated with disease progression. Commercial diagnostic kits are available to diagnose these biomarkers and are calibrated according to diagnostic needs.

KEYWORDS: A biomarker is naturally occurring molecule or gene or characteristic.

INTRODUCTION

Periodontitis is a group of inflammatory diseases that affect the connective tissue attachment and supporting bone around the teeth.[1] 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.[2]

A goal of periodontal diagnostic procedures is to provide useful information to the clinician regarding the present periodontal disease type, location, and severity.[3] Traditional periodontal diagnostic parameters used clinically include probing depths, bleeding on probing, clinical attachment levels, plaque index, and radiographs assessing alveolar bone level.[4] 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. 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.[3]

Predictors of Periodontal Disease

1. Risk Factors – An event that is related statistically in some way to an outcome of a disease.
2. Risk Marker – An attribute associated with increases probability of having disease.
3. Risk Determinant – An event that increases probability of occurrence of disease.
4. Risk Indicators – An event that is associated with an outcome in cross sectional studies.
5. Biomarkers - A characteristic that can be measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacologic responses to therapeutic interventions.

Need For a Periodontal Diagnostic Indicator

The diagnosis of active phases of periodontal disease and the identification of patients at risk for active disease are challenges for clinical investigators and practitioners alike.[5] Researchers are confronted with the need for innovative diagnostic tests that focus on the early recognition of the microbial challenge to the host. Optimal innovative approaches would correctly determine the presence of current disease activity, predict sites vulnerable for future breakdown and assess the response to periodontal interventions.[6] A new paradigm for periodontal diagnosis would ultimately improve the clinical management of periodontal patients.[7]

Assessing potential biomarkers of periodontal disease activity

Conventional clinical and radiographical methods of periodontal diagnosis are only capable of retrospective

diagnosis of attachment and bone loss; these are unable to either detect or predict periodontal disease activity. For these reasons a large proportion of recent periodontal research has been concerned with finding and testing potential markers of periodontal disease activity. A periodontal diagnostic tool provides pertinent information for differential diagnosis, localization of disease, and severity of infection. These diagnostics, in turn, serve as a basis for planning treatment and provide a means for assessing the effectiveness of periodontal therapy. There is a need for developing new diagnostic kits that can detect active disease, predict future disease progression & evaluate response to periodontal therapy, thereby improving clinical management of periodontal patients, which still remains a challenge to clinical investigators and practitioners.[3]

Diagnostic Kits

Ideal Requisites

1. Diagnostic when applied should result in minimal perturbation of the sampled region, since flow or volume changes can quantitatively alter the composition of biochemical constituents present.
2. The measurement should be a simple, single stage procedure that directly and rapidly assesses disease state in vivo & include as many biomarkers associated with disease as possible to maximize the specificity and selectivity of the measurement.
3. The detection method should be inexpensive, robust & ultimately designed for chairside testing.
4. The test should have high sensitivity and specificity when assessing a particular biomarker.

Four potential sources are available

Because 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.[8] 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.[9] Many studies have shown that the determination of inflammatory mediator levels in biologic fluids is a good indicator of inflammatory activity. Therefore, studies related to the pathogenesis of periodontal diseases usually examine whether biochemical and immunologic markers in saliva or GCF might reflect the extent of periodontal destruction and possibly predict future disease progression.[8] Oral fluid biomarkers that have been studied for periodontal diagnosis include proteins of host origin (i.e., enzymes and immunoglobulins), phenotypic markers, host cells, hormones, bacteria and bacterial products, ions, and volatile compound.[8]

Potential GCF biomarkers of periodontal disease activity

1. Subgingival bacteria and their products
2. Hydrolytic enzymes released from Immune cells
3. Inflammatory and Immune products
4. Enzymes released from dead cells
5. Connective tissue degradation products
6. Products of bone resorption

Potential microbiological Markers

Of the more than 600 bacterial species that have been identified from subgingival plaque, only a small number have been suggested to play a causal role in the pathogenesis of destructive periodontal diseases in the susceptible host.[10] Furthermore, technologic advances in methodologies such as analysis of 16S ribosomal RNA bacterial genes indicate that as many as several hundred additional species of not-yet-identified bacteria may exist.[11] The presence of bacteria adjacent to the gingival crevice and the intimate contact of bacterial lipopolysaccharide with the host cells trigger monocytes, polymorphonuclear leukocytes (neutrophils), macrophages, and other cells to release inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor (TNF)-a, and prostaglandin E2.[12]

Methods of detecting bacteria

1. Bacterial culture
2. Phase contrast Microscopy
3. Immunological assays
4. DNA Probes
5. Enzyme based assays

Commercial diagnostic test kits available

1. Evalusite (Kodak) – Identifies and quantitates A.actinomycetemcomitans, P.gingivalis & P.intermedia.
2. Omnigene (OmniGene, Inc) and BTD (Biotechnica Diagnostics, Inc) - A.actinomycetemcomitans, P.gingivalis & P.intermedia, & T. denticola.
3. Perioscan (Oral-B Laboratories) - Detection of the trypsin – like protease produced mainly by P. gingivalis, T. forsythus and T. denticola.
4. TOPAS Kit – Assesses total toxin and protein levels.

Potential inflammatory and immune markers

Periodontal inflammation occurs in the gingival tissue in response to plaque bacteria biofilms.[12] Gingivitis is characterized by an initial increase in blood flow, enhanced vascular permeability, and the influx of cells (neutrophils and monocyte-macrophages) from the peripheral blood to the gingival crevice.[13] Subsequently, T cells and B cells appear at the infection site. After they appear at the lesion, these cells produce a myriad of cytokines such as IL-1b, IL-6, TNF-a, and immunoglubulins as an antigen specific response. Initially, tissue degradation is limited to epithelial cells and collagen fibers from the connective tissue. Later on, the inflammatory process may reach periodontal supportive tissue, leading to bone resorption.[14]

Biomarkers of Immune Response

1. Antibodies
2. Complement system

Biomarkers of Inflammatory response
1. Arachidonic acid derivative like PGE2
2. Cytokines like IL-1, IL-2, IL-4, IL-6 and TNF-α

Proteolytic and hydrolytic enzymes of inflammatory cell

Proteolytic Enzymes
1. Collagenase
2. Cathepsin G
3. Cathepsin B
4. Cathepsin D
5. Dipeptidylpeptidases
6. Tryptase
7. Hydrolytics Enzymes:
8. Aryl Sulphatase
9. B – Glucuronidase
10. Alkaline Phosphatase
11. Acid Phosphatase
12. Myeloperoxidase
13. Lysozyme
14. Lactoferrin

Commercial diagnostic kits for GCF proteolytic and hydrolytic enzyme levels
1. Periocheck (ACTech) – neutral protease like Collagenase, Elastase.
2. Prognostik (Dentsply) – serine Proteinase & Elastase.
3. Protek - bacterial Proteases like arg-gingipain and Dipeptidylpeptidase
4. B-glucoronidase diagnostic kit (Abbott Laboratories, North Chicago, USA)

Markers of Connective Tissue Degradation

Connective tissue
1. Collagen I, III, V
2. Proteogycans (GAGs)
3. Hyaluron
4. Fibronectin
5. Basement Membrane
6. Collagen IV
7. Laminin

Commercial diagnostic aids available
1. High presence liquid chromatography – Hydroxyproline.
2. Iron exchange chromatography – Hydroxyproline.
3. Cellulose acetate extraction and staining – Glycoraminoglycans.

Potential markers of cell death & tissue degradation
1. Aspartate amino transferase
2. Lactate dehydrogenase

Commercial diagnostic aids available
1. Pocketwatch (Steri-Oss, Yorba Linda, CA) – Aspartate amino transferase
2. Periogard (Colgate) – Aspartate amino transferase.

Potential markers of bone resorption

Of the 50 or more different components in GCF and saliva evaluated to date for periodontal diagnosis, most lack specificity to alveolar bone destruction and essentially constitute soft tissue inflammatory events[15]. When examining the destruction of alveolar bone that is preceded by a microbial infection and inflammatory response, the measurement of connective tissue derived molecules may lead to a more accurate assessment of tissue breakdown due to the tremendous variability of the host response among individuals.[15]

Bone specific proteins
1. Osteonectin
2. Bone phosphoprotein (N-propeptide)
3. Osteocalcin
4. Telopeptides of type I collagen (CTP)
5. Collagen I
6. Proteoglycans

Commercial diagnostic aids available
1. Osteocalcin - ELISA/Radioimmunoassays.
2. CTP – radioimmunoassay.
3. Osteonectin and N-propetide – Elisa.

Salivary Biomarkers

Saliva is a most valuable oral fluid that often is taken for granted. It is sad, but true. Dentists as well as physicians know very little about saliva. Salivary gland secretions contain locally produced proteins, as well as other molecules from the systemic circulation. It is this rich mixture of substances that makes saliva a likely source for identifying unique biomarkers that reflect oral and systemic health changes. The challenge of salivary diagnostics is to discover its potential and optimize engineering technologies for use with this biofluid. Researchers envision that some of human health and disease states will be reflected diagnostically in saliva via proteomic or genomic information.[16]

Advantages
1. Saliva is a readily available fluid and contains locally produced microbial and host response mediators as well as systemic markers.
2. These markers help to analyse the current status of disease activity.
3. Can be collected more easily, with non invasive procedures and with minimum patient discomfort.
4. Salivary diagnostic tests are applicable for screening large populations.

Disadvanages
1. Complex origin and derivation from variety of sources.
2. Salivary secretion rate has a dilution effect that can prevent detection of a potentially discriminating diagnostic factor.
3. Considerable variation in the concentration of substances is also observed routinely in health as well as periodontally diseased subjects.

Future directions

There is a plethora of possibilities for the future use of oral fluids in biotechnology and health care applications, especially in the field of diagnostics. A tremendous amount of research activity is currently under way to explore the role of oral fluids as a possible medium in a variety of applications.[3]

CONCLUSION

Biomarkers may serve as a tool to monitor and predict susceptibility to periodontal disease. The sequestering and/or degradation of possible biomarkers may limit the detection of the absolute concentration of each biomarker. Future, longitudinal well-controlled clinical trials are needed to find reliable biomarkers for periodontal diagnosis and to determine future risk of disease.

REFERENCES

1. Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: current concepts. J Periodontol, 1992; 63(4 Suppl): 322–31. Vvv Mario Taba et al, Diagnostic Biomarkers for Oral and Periodontal Diseases. Dent Clin N Am 49, 2005: 551–571.
2. Genco RJ. Host responses in periodontal diseases: current concepts. J Periodontol, 1992; 63(Suppl 4): 338–55.
3. Taba M, Kinney J, Kim AS, Giannobile WV. Diagnostic Biomarkers for Oral and Periodontal Diseases. Dental clinics of North America. 2005;49(3):551-vi. doi:10.1016/j.cden, 2005; 03: 009.
4. Armitage GC. The complete periodontal examination. Periodontol 2000, 2004; 34: 22–33.
5. Souza SL, Taba M Jr. Cross-sectional evaluation of clinical parameters to select high prevalence populations for periodontal disease: the site comparative severity methodology. Braz Dent J, 2004; 15(1):46–53.
6. Subrahmanyam MV, Sangeetha M. Gingival Crevicular Fluid A Marker of the Periodontal Disease Activity. Indian J Clin Biochem, 2003; 18: 5–7.
7. Kinney JS, Ramseier CA, Giannobile WV. Oral fluid-based biomarkers of alveolar bone loss in periodontitis. Ann N Y Acad Sci, 2007; 1098: 230–51.
8. Kaufman E, Lamster IB. Analysis of saliva for periodontal diagnosis—a review. J Clin Periodontol, 2000; 27(7): 453–65.
9. Zambon JJ, Nakamura M, Slots J. Effect of periodontal therapy on salivary enzymatic activity. J Periodontal Res, 1985; 20(6): 652–9.
10. Socransky SS, Haffajee AD. Dental biofilms: difficult therapeutic targets. Periodontol 2000, 2002; 28: 12–55.
11. Paster BJ, Boches SK, Galvin JL, et al. Bacterial diversity in human subgingival plaque. J Bacteriol, 2001; 183(12): 3770–83.
12. KirkwoodKLTabaMJrRossaCNewmanMTakeiHMol ecular biology of the host-microbe interaction in periodontal diseases. Selected topics: molecular signaling aspects of pathogen-mediated bone destruction in periodontal diseases. Carranza's periodontologyElsevierSt. Louis (MO)10th; in press.
13. Madianos PN, Papapanou PN, Sandros J. Porphyromonas gingivalis infection of oral epithelium inhibits neutrophil transepithelial migration. Infect Immun, 1997; 65(10): 3983–90.
14. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. Lab Invest, 1976; 34(3): 235–49.
15. Giannobile WV. C-telopeptide pyridinoline cross-links. Sensitive indicators of periodontal tissue destruction. Ann N Y Acad Sci, 1999; 878: 404–12.
16. Khiste SV, Ranganath V, Nichani AS, Rajani V. Critical analysis of biomarkers in the current periodontal practice. Journal of Indian Society of Periodontology, 2011; 15(2): 104-110.