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Review Article

Biomarkers in periodontal health and diseases

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ABSTRACT

Cause of tooth loss in world is periodontitis which is a bacterial infection whose pathogenesis has complex immune response. The diagnosis is based upon patient's periodontal health, full mouth bleeding score, full mouth plaque score, probing depth, clinical attachment level, bleeding on probing, recessions, mobility, and migration. For early diagnosis of periodontitis chair side diagnostic tests are available which are used by periodontist. There are many biomarkers for periodontitis which help in early detection like: MMP-8 (Metalloproteinase-8), MIP-1α (Macrophage inflammatory protein-1 alpha), IL-1 β (Interleukin-1beta), IL-6 (Interleukin-6), and HB (Hemoglobin), and their combinations.

1. Introduction

Periodontal disease is multifactorial and is a complex disease therefore its diagnosis, prevention and management are issues which, if treated effectively, can yield considerable healthcare benefit. Despite understanding the pathogenesis of periodontitis it still considered as connective tissue and bone destruction. Furthermore, monitoring its progression is a highly skilled and technically demanding process involving measurement of bleeding on probing, probing depth and attachment loss coupled with radiographic assessment and (subjective) visual observations. The introduction of biomarkers for identifying periodontal disease would be highly desirable as the current diagnostic approaches do not reflect current disease activity. Biomarkers are indicators with high prognostic and predictive value. They must be able to detect the presence of a disease or its progression.[1]

2. Limitations of Traditional Periodontal Diagnostic Techniques

1. Clinical and radiological measurements of attachment loss are not precisely accurate.
2. Full mouth recording is necessary because of the site specific nature of periodontal disease progression.
3. Individual susceptibility to periodontitis varies both genetically and over time.
4. All clinical diagnostic techniques provide information about past disease activity and are unable to diagnose present disease activity.[2]

3. What is a Biomarker

It is a term used to describe medical signs, that is indicative of medical state observed from outside the patient, which can be measured accurately and reproducibly. In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined, biomarker as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

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Table 1: Classification of biomarkers

Proteomic biomarkers	Genetic biomarkers	Microbial biomarkers	Other biomarkers
Cystatins, αglucoronidase, Acid phosphatase, alkaline phosphatase, lactoferrin, IgM, MMP-13, MMP-9, MMP-8, Osteocalcin, Osteopontin, Elastase, Platelet activating factor, epidermal growth factor, Platelet derived growth factor, carboxytelopeptidase type- I	Cathepsin C gene mutation, Collagen gene mutation, Interleukins, Tumor necrosis factor	Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Mycoplasmas, Porphyromonas gingivalis, Prevotella intermedia, Peptostreptococcus Micros, Prevotella nigrescens, Treponema denticola, Tannerella forsythia. Treponema socransky	Calcium, Cortisol, Hydrogensulphide, Methylmercaptan, Pyridine.

In 2001 World Health Organization (WHO) and in coordination with the United Nations and the International Labour Organization, has defined a biomarker as 'any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease'.[3]

3.1. Proteomic biomarkers

It is an entire complement of proteins which involves enzymatic digestion of whole protein into small fragments for detection of numerous tumors and inflammatory diseases. Proteomic analysis have become essential tools in oral sciences especially in periodontology. Proteins such as cathepsin B have been found in chronic periodontitis, MMP's are involved in degradation of PDL and protein kinases play a significant role in inflammatory process in periodontal diseases.[4]

3.2. Immunoglobulins

Periodontal pathogens give rise to humoral immune response which leads to production of antibodies. Measurement of these antibodies can be helpful in diagnosis of periodontitis, estimation of its activity, classification and the success of treatment. In periodontitis IgG class antibody are persistently elevated. Also, high serum IgA class antibody levels can be measured in severe periodontitis during acute disease phase.[5]

3.3. Osteocalcin and fibronectin

These are connective tissue breakdown products and are markers for bone homeostasis. They are associated with bone remodeling and also seen in systemic conditions like osteoporosis and metastatic bone cancer.[6]

3.4. Acid phosphatase

They are released from inflammatory cells in the GCF. Levels however do not correlate with the disease severity or activity.[7]

3.5. Alkaline phosphatase

It plays a role in bone metabolism and is found in PMN's. It has been seen associated with deeper pocket depths. And is found in diseased sites rather than healthy sites.[7]

3.6. Carboxytelopeptidase type-I collagen

Products of degradation released during breakdown of collagen matrix and during bone resorption. Pyridinoline, deoxypyridinoline, N-telopeptides, and C-telopeptides are common biomarkers for bone turnover and are specific for periodontal disease.[6]

3.7. Osteopontin

It is produced by osteoblasts, osteoclasts and macrophages and is a non-collagenous calcium binding glycosylated phosphoprotein present in the bone matrix.

3.8. Matrix metalloproteinases

They are capable of cleaving extracellular, pericellular and non matrix substrates. MMP's can be divided into four different subfamilies according to their primary structures and substrate specificities: collagenases, gelatinases, membrane type MMP's and others. Main function of MMP's is to degrade extracellular matrix component in tissue remodeling and turnover during physiological development. Major MMP's seen in periodontitis are MMP-8 and MMP-9 derived from neutrophils and MMP-13 derived from epithelial and bone cells.

4. Platelet-Derived Growth Factor (PDGF)

They have fibroblast proliferative activity. It is mainly seen in pocket epithelium and inflamed gingiva. It stimulates fibroblast to synthesize proteoglycans for development of extracellular matrix.

4.1. Vascular endothelial growth factor (VEGF)

It contributes in periodontal healing by regulating angiogenesis, vascular permeability and endothelial

cell proliferation. It is commonly found in neutrophils, plasma cells and junctional epithelium.

5. Genetic Biomarkers

5.1. Interleukin polymorphism

Gene polymorphism of cytokines, chemokines, receptors and enzymes play essential role in innate, immune and inflammatory response. Interleukins like IL-4, IL-6 and IL-10 are most commonly involved in periodontitis. IL-1α, IL-1β are proinflammatory agents and plays essential role in initiating and regulating the pathogenesis of periodontitis. They bind to the specific receptor and leads to the alveolar bone resorption and extracellular matrix degradation.[8]

5.2. Cathepsin c polymorphism

It seems to play important role in immunopathology of periodontal disease. Polymorphism with these genes may be related to changes in protein expression, structure and function. Thus, these genes may affect the severity of periodontitis.[9]

5.3. Tumor necrosis factorα gene polymorphism

It has a high potential for bone resorption. This mechanism is based on stimulation of osteoclasts and enhancing maturated osteoclasts activity. Has a critical role in bone resorption.[10]

5.4. CD14 gene polymorphism

Cluster differentiation 14 is a toll like receptor which act as a first gate in recognition of periopathogens by host. Helps in release of various proinflammatory cytokines and leads to bone resorption.[10]

5.5. Microbial biomarkers

There are number of periodontal species present in subgingival plaque but only few of them are causing periodontal disease. Specific periodontal pathogens include Tanerella forsythensis, Porphyromonas gingivalis and Treponema denticolla. These are members of red complex bacteria and are highly implicated in progression of periodontal diseases. Actinobacillus actinomycetemcomitans is associated with early forms of periodontal disease whereas red complexes are associated with chronic periodontitis.[11]

6. Other Biomarkers

6.1. Cortisol

There is a relationship between periodontitis and psyhco-neuroimmunological parameter such as cortisol has been seen. Cortisol is released by HPA axis which leads to increase glucose levels through gluconeogenesis.[12]

6.2. Calcium

It has been seen that there are different salivary calcium levels in periodontitis patients than healthy subjects. High salivary calcium group has more intact teeth than their pairs in low salivary calcium group.[13]

6.3. Volatiles

Volatile sulfur compounds especially hydrogen sulfide and methylmercaptan are associated with oral malodor. They have been suggested as possible diagnostic markers in periodontal disease.

6.4. Chairside biomarkers detection

Microbial dark matter obtained from clinical sites of infection was not earlier visible by conventional methods. It becomes important to identify these microbial trends that occur in different stages of periodontal diseases. With regard to periodontal diagnosis some basic approaches have been developed for detection of biochemical or molecular factors in fluids such as saliva or GCF. For example detection of Matrix metalloproteinases in biological fluids can help in detection of undiagnosed periodontitis. Various physical methods have been developed such as broad-spectrum fluorescence resonance energy transfer which measures the protease activity in saliva, Infrared attenuated total reflection which measures the inter-individual differences in saliva. These properties help in identifying patients of low to high risk patients.[14]

With the understanding of pathogenesis of periodontal diseases various biomarkers have been detected which serves important role in pathogenesis of periodontal diseases. They help in identifying periodontal pathogen and evaluation of prognosis after treatment. Various biomarker assay kits are available like biochemical assay kits, Microbiological assay kits and Genetic assay kits.

In dental practice the knowledge of these biomarkers help in early diagnosis and monitoring of periodontal diseases. For instance, constituents presents in saliva provide complimentary diagnostic information that have the potential for point of care use by dental professionals and general public. As it is with other fluids, high levels of IL-1β, IL-8, MMP-8, MIP-1α, OPG and TNF-α can be seen also in saliva of the patients with chronic periodontitis. These biomarkers are actively involved in inflammation, connective tissue degradation and alveolar born turnover. Providing proper treatment like SRP to these patients help in significant reduction of these biomarkers. Hence, biomarkers reflect the status of periodontal disease in patients who receive mechanical periodontal therapy.[16,17]

Table 2: Examples of biomarker assay kits [15]

Biomarker classification	Product name	Detecting target
Biochemical assay	Periocheck	Neutral proteases
	Pocket watch	Aspartate aminotransferase
	Perioguard	Aspartate aminotransferase
	Periosafe	Active Matrixmetalloproteinases
Microbiological assay	Evalusite	Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Provotella intermedia
	BANA-Enzymatic test kit	
Genetic assay	PerioPredict	Genes for IL-1
	MyPerioID	Genes for IL-6

7. Conclusion

Biomarkers have a significant role in pathogenesis of the periodontal disease. There is requirement of reliable biomarkers in that can help in distinguishing progressive periodontitis cases from normal biological processes. Concept is to monitor health status, disease susceptibility, progression, resolution and treatment outcome. Biomarkers are indicative of physiological health, pathological health and response to therapy. There is also need to develop practical approach to chairside analysis which will help to efficiently and accurately assess periodontal disease activity.

8. Conflict of Interest

None.

9. Source of Funding

None.

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