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Importance of Biomarker Research in Periodontics

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Abstract

A variety of dental and periodontal indices and parameters are used along with radiographs for the purpose of diagnosis and assessment of alveolar bone levels in periodontitis patients. The future research is currently working towards development of objective measures such as biomarkers which can identify and quantify periodontal disease risk and its progression. Biomarkers are used to objectively evaluate normal biologic processes, pathogenic processes and pharmacologic response to therapy protocols. Biomarkers are tell-tale molecules that could be used to monitor health status, disease onset, treatment response and outcome. Biomarkers serve as early surveillance of periodontal disease.

Keywords

Periodontal disease; Biomarkers; Periodontal diagnosis

Introduction

Periodontal diseases affect the supporting structures around the teeth. 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 [1-3].

Diagnostic parameters should provide the clinician with information regarding the exact status of the disease, focusing on the disease type, severity and location. These findings serve as a basis for treatment planning and the maintenance phase performed by the patient following treatment. Common parameters used for periodontal diseases include probing depth, clinical attachment levels, dental indices such as plaque index and radiographic assessment [4].

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. Biomarkers objectively measure or indicate the normal physiologic, pathologic status of a disease and also the response from this therapeutic intervention. Biomarkers are tell-tale molecules that could be used to monitor health status, disease onset, treatment response and outcome. Informative biomarkers can further serve as early sentinels of disease [5,6]. A biomarker or biologic marker, according to the most recent definition [7], is a substance that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Before employing the use of any biomarker, it is essential to understand their relation to disease progress and therapy protocols.

Practitioners and investigators face a challenge with identifying patients at risk of active disease and diagnosing the active phases of periodontal disease [8]. Biomarkers can be used to resolve this challenge. Saliva and GCF are oral fluids which are usually used for biomarker analysis.

What are the Microbial Factors for Diagnosis of Periodontal Disease?

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, other cells to release inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, and prostaglandin E2 [8].

A systematic review of this topic reveals that the literature lacks studies with a high evidence rating; the most-pertinent studies were case reports or case series without controls [9].New strategies that combine microbial identification with host response or tissue breakdown factors using discriminate analysis may improve the ability of microbial analysis to predict future periodontal diseases.

What are the Host Response and Inflammatory Mediators which can be used as Biomarkers?

Periodontal inflammation occurs in the gingival tissue in response to lipopolysaccharide (LPS) from plaque bacteria biofilms and leads to a cascade of events. Pathogens present in plaque biofilm activate chemotaxis of polymorphonuclear leucocytes (PMN) as a first line of defense against infection. Monocytes and activated macrophages respond to endotoxin by releasing cytokines (tumor necrosis factor [TNF] and interleukin 1 [IL1]) that are mediators for bone resorption. Fibroblasts release matrix metalloproteinases (MMPs). These act along with the PMNs in destruction of collagen. TNF, IL-1, and receptor activator of NF-kB ligand (RANKL) are elevated in disease sites and play an important role in osteoclastogenesis and bone resorption. Pyridinoline cross-linked carboxy terminal telopeptide of type I collagen are tissue degradation molecules also play a role in bone resorption. These are released in the GCF and can be used as biomarkers along with other cytokines and enzymes such as RANK, receptor activator of NF-kB [10,11].

GCF has been extensively investigated for the release of host response factors. Host cell-derived enzymes such as matrix metalloproteinases (MMPs) are implicated in the destructive process of periodontal disease that can be measured in GCF. Kinane, et al [12] and Mantyla, et al [13] presented the use of a rapid chair side test based on the immunologic detection of elevated MMP-8 in GCF to diagnose and monitor the course and treatment of periodontitis. Holmlund, et al [14] investigated bone resorption activity, IL-1α, IL-1β, and IL-1 receptor antagonist levels in GCF in sites having no periodontal disease and having horizontal or angular periodontal bone loss using ELISA. It was observed that levels of bone resorption activity, IL-1α, IL-1β, and IL-1 receptor antagonist were significantly higher in GCF from diseased sites compared with healthy sites Aspartate aminotransferase-positive sites are positively correlated with higher prevalence of periodontal pathogens [15]. They are released from necrotic cells in GCF and are associated with periodontitis severity.

What are the Bone-Specific Biomarkers for Periodontal Diagnosis?

Advances in bone cell biology over the past decade have resulted in several new biochemical markers for the measurement of bone homeostasis. With mounting evidence for a relationship between osteoporosis and oral bone loss, investigators have sought to develop better biologic markers to determine and predict oral bone loss [16] These include bone collagen fragments and osteocalcin.

What does the Future Hold?

Oral fluids have been used for the purpose of HIV diagnosis. A commercially available kit (OraSure, OraSure Technologies, Bethlehem, Pennsylvania) has an oral specimen collection device to collect HIV-1 antibodies (not the virus) from thetissues of the cheek and gingival. It does not collect saliva but a sample called oral mucosal transudate. For different fluids (oral fluid, finger-stick or venipuncture whole blood or plasma specimens), the alternative test OraQuick (OraSure Technologies) provides accurate results for HIV-1 and HIV-2 in 20 minutes [17,18]. Li et al. [19] investigated the potential use of genomics in the development of salivary diagnostics. They performed microarray testing of cell-free saliva for RNA profiling. RNA was isolated from unstimulated saliva that was collected from healthy subjects. After analysis by microarray and quantitative polymerase chain reaction, they found that it was possible to profile messenger RNAs, of which there were thousands present in the saliva. More recently, the group

demonstrated the potential of salivary IL-8 levels to predict patients afflicted with squamous cell carcinoma [19]. Salivary immunocomponents have also been studied at length in oral health, including immunoglobulin subclass, immunoglobulin isotypes, and antibody levels. Other salivary constituents that have been investigated for diagnostic uses include epithelial keratins [20], occult blood [21], and salivary ions such as calcium and phosphates, and serum markers such as cortisol [22]. Proteomics presents as a novel science and shows immense potential in this field. In contrast to gene expression studies employing oligonucleotide chips ('transcriptomics'), proteomics directly addresses the level of gene products present in a given cell state and can characterize protein activities, interactions and sub cellular distributions. Scientists are very interested in proteomics because it gives a much better understanding of an organism than genomics.

- Transcription levels of a gene do not provide information on protein expression. An mRNA produced in abundance may be degraded rapidly or translated inefficiently, resulting in a small amount of protein.
- Post-translation modifications also play a role in protein expression and function. Phosphorylation is sometimes required for the protein to become active. Glycoproteomics and phosphoproteomics study these post-translational modifications.
- Many transcripts give rise to more than one protein, through alternative splicing or alternative post-translational modifications.
- Some protein complexes are formed acting with other proteins or RNA molecules. These complexes can function only in the presence of the other molecules.
- Protein degradation rate plays an important role in protein content.

In a scenario where oral micro-organisms are adapting to changing environments, proteomics provides with a novel way to understand and adapt to these changes (Table 1).

Risk Marker	An attribute or event that is associated with increased probability of disease but is not necessarily a causal factor.
Risk Indicator	An event that is associated with an outcome only in cross-sectional studies.
Risk Factor	An action or event that is related statistically in some to an outcome and is truly causal.
Risk Determinant	An attribute or event that increases the probability of occurrence of disease.
Biomarker	A substance that is measure objectively and evaluated as an indicator of normal biologic processes , pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Table 1: Important related terminologies.

Conclusion

Biomarkers can be used to monitor health status, disease risk and onset, and outcome response to treatment in normal healthy individuals and individuals affected by specific diseases. New diagnostic technologies, such as microarray and micro fluidics, are available for risk assessment and screening of

biomarkers. The use of proteomics and gene expression will advance the diagnosis and treatment of various oral pathological conditions to reach the above goals and also advances in tissue engineering, drug delivery, gene therapy and biopharmaceuticals will present new therapeutic opportunities leading to individualized, specific &targeted treatment of periodontal diseases.

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