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Salivary Biomarkers

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ABSTRACT
Various diseases of the oral cavity can be diagnosed from the oral fluids. Such diagnosis can be imagined because our medical field has progressed in many ways. One of the major progress can be visualized in the area of detection of diseases using saliva. The important diagnostic materials present in saliva such as salivary biomarkers, not only guide in the detection of oral diseases but can be used to evaluate the systemic diseases. This article is a review of the earlier studies which discusses about the different kind of biomarkers present in saliva and their role in diagnosing various diseases and conditions. Therefore, saliva is the promising aid in the diagnosis of chronic periodontal disease1.

Introduction

PERIODONTAL disease is a diseases that, ”affect the gingiva and the supporting connective tissue and alveolar bone, which anchor the teeth in the jaws. The periodontal disease is one of the most common chronic pathological conditions of mankind that have affected since ages. Periodontal diseases (PD) are chronic infectious inflammatory diseases characterized by the destruction of tooth-supporting structures, being the presence of periodontopathogens required, but not sufficient, for disease development. However, host inflammatory mediators have been associated with tissue destruction, 3.. The significant feature of this disease is that “it starts with bacteria surrounding the surface of tooth, especially the gingival sulcus and then interferes with host response leading to destruction of bone and surrounding tissues.” After its initiation, the disease progresses with the loss of collagen fibers and attachment to the cemental surface, apical migration of the junctional epithelium, formation of deepened periodontal pockets, and resorption of alveolar bone. Overtime if the process is let to continue, the disease continues with progressive bone destruction, leading to tooth mobility and subsequent tooth loss. The periodontal disease afflicts above 90% of the adult population in the (do not add in the) worldwide, with approximately 10% displaying severe disease concomitant with early tooth loss.

A goal of periodontal diagnostic procedures is to provide necessary information to the clinician regarding the present periodontal disease type, location, and severity. These findings serve as a basis for treatment planning and provide essential data during periodontal maintenance and disease-monitoring phases of treatment. (5).

Traditional periodontal diagnostic parameters used clinically include probing depths, bleeding on probing, clinical attachment levels, plaque index, and radiographs assessing alveolar bone level. The traditional tools brought efficiency in time, cost and made the procedure less invasive. But their limitations soon came to be seen in the fact that only history of the disease could be observed while the current condition is often left misdiagnosed. Clinical attachment loss readings by the periodontal probe and radiographic evaluations of alveolar bone loss measure damage from past episodes of destruction and require a 2- to 3-mm threshold change before a site can be identified as having experienced a significant disease. 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.

Advantages of traditional diagnostic techniques

Easy to use, Cost effective, Non-invasive, Measures disease severity

Limitations of traditional periodontal diagnostic techniques

a) Clinical and radiological measurements of attachment loss are not precisely accurate

b) Full mouth recording is necessary because of the site specific nature of periodontal pathogens.

c) Individual susceptibility to periodontitis varies both genetically and over time.

d) All clinical diagnostic techniques provide information about past clinical picture and are unable to detect present degeneration.

Salivary Biomarker

A biomarker or biologic marker, 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. Because saliva and GCF are fluids easily collected and contain locally and systemically derived markers of chronic periodontitis, they may offer the basis for a patient-specific biomarker assessment for periodontitis and other systemic diseases (7).

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The diagnostic use of salivary biomarkers poses several advantages over the traditional measurements of inflammatory biomarkers in blood. For example, (i) they not only relieve the patients of the stress of needle and pain, but also eliminate the need of specialized technicians for specimen collection, thereby reducing the healthcare costs; (ii) they do not clot, and therefore eliminate the need of anticoagulation treatment after collection; (iii) they are less likely to transmit diseases than blood through contact or needle-stick injury and therefore are safer; (iv) their molecular activity doesn't change much after sampling; (v) they are a relatively clean medium and contain few interfering proteins; and (vi) the simplicity of specimen collection opens an avenue for self-collection of specimens at home by the patients.7 The future potential by which patients can assess themselves at home with prior education also makes this method better than the traditional one.

Saliva as a diagnostic fluid

Saliva is important physiologic fluids containing a highly complex mixture of substances including proteins and genetic molecules. Saliva provides non-invasiveness and stress-free sample collection, easy and multiple sampling opportunities, reduced need for sample pre-processing, and minimal risk of contracting infectious organisms, and it is also an ideal biofluid for collecting specimens from patients in developing countries. 7

Whilst blood and GCF were previously the biological indicators of inflammation, saliva has recently gained more attention as a readily accessible oral fluid which has a mediator profile like that of serum and gingival crevicular fluid. This review article aimed at providing a comprehensive overview of salivary cytokines in periodontitis, highlighting extensively studied cytokines such as interleukin-1beta and interleukin-6, but also cytokines that have been the subject of only a few studies and which warrant further investigation -8

Research into biomarkers of periodontitis is driven by mainly three objectives:

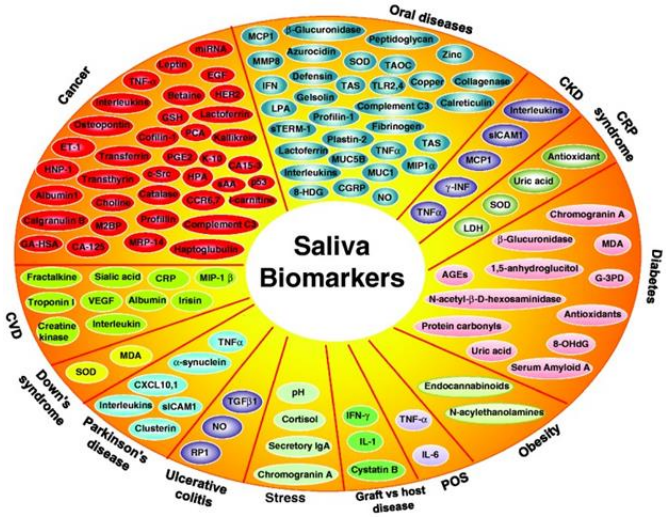
1. To identify 'at risk' patients before periodontal tissue destruction
2. To determine disease activity and progression;
3. To build up our understanding of this wide spread disease with the purpose of finding new therapy.

Salivary Biomarkers: Material and methods

Detecting pathologies at their earliest stages can significantly affect patient discomfort, prognosis, therapeutic intervention, survival rates, and recurrence. Diagnosis and monitoring often require painful invasive procedures such as biopsies and repeated blood draws, adding undue stress to an already unpleasant experience. The discovery of saliva-based microbial, immunologic, and molecular biomarkers offers unique opportunities to bypass these measures by utilizing oral fluids to evaluate the condition of both healthy and diseased individuals. Here we discuss saliva and its significance as a source of indicators for local, systemic, and disease.9

1. Cytokines

Cytokines are soluble proteins that bind to specific receptors on target cells and initiate intracellular signaling cascades resulting in phenotypic changes in the cell via altered gene regulation. They are effective at low concentrations, are produced transiently in the tissues in which they are produced, induce their own expression in an autocrine or paracrine fashion, and have pleiotropic effects on a large number of cell types. [4] I*nterleukin-1*



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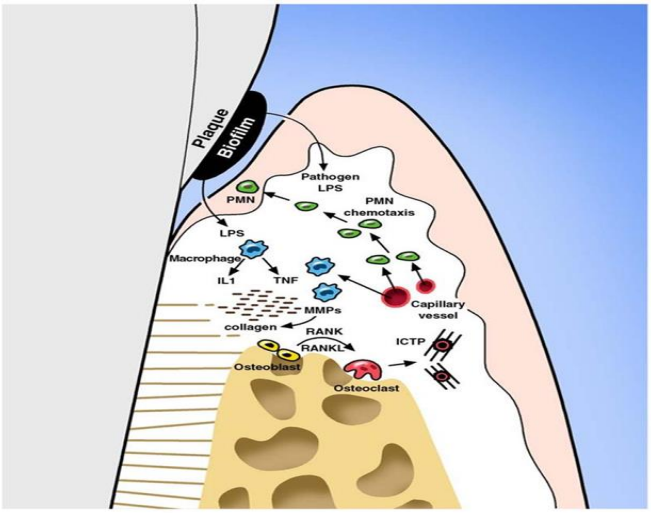
Cytokines and selective inflammatory mediators play crucial roles in the maintenance of tissue homeostasis, a process that which requires a delicate balance between anabolic and catabolic activities. [3] In particular, growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor-β (TGF-β) are thought to play important roles in modulating the proliferation and migration of structural cells in the periodontium and the production of various extracellular matrices by these cells. There is little doubt that excessive and continuous production of cytokines in inflamed periodontal tissues is responsible for the progress of periodontitis and periodontal tissue destruction. Particularly, inflammatory cytokines such as interleukin (IL)-lα, IL-β, IL-6, and IL-8 are present in the diseased periodontal tissues, and their uncontrolled production seems to play a role in chronic leukocyte recruitment and tissue destruction. [1] The factors included in the cytokine molecule group are ILs, interferons, growth factors, cytotoxic factors, activating or inhibitory factors, colony stimulating factors, and intercrines. [1] As a rule, the synthesis of cytokines is inducible, although some factors are known to be produced constitutively. The mechanisms by which cytokines act on the target cells are classified into four types: autocrine, intracrine, juxtacrine, and paracrine. 10

a) Interlukin 1

Interleukin-1 (IL-1) is the prototypic pro-inflammatory cytokine. There are two types of IL-1, IL-1alpha and IL-1beta and in majority studies, their biological activities are indistinguishable. IL-1 affects nearly every cell type, often in concert with another pro-inflammatory cytokine, tumor necrosis factor (TNF). Although IL-1 can upregulate host defenses and function as an immunoadjuvant, IL-1 is a highly inflammatory cytokines 8 IL-1 is known to stimulate the proliferation of keratinocytes, fibroblasts, and endothelial cells and to enhance fibroblast synthesis of type I procollagen, collagenase, hyaluronate, fibronectin, and prostaglandin E2 (PGE2). The local excessive production of IL-I by cells composing the periodontium appears to be capable of stimulating gingival and PDL fibroblasts, in an autocrine or paracrine fashion, to induce the production of other cytokines, matrix-degrading enzymes, and PGE2. These mediators may be responsible for effecting connective tissue destruction, leading to the loss of attachment. Thus, IL-1 has been suggested to play a key role in promoting alveolar bone destruction in periodontal disease. [1] There is evidence that

susceptibility to periodontal disease is influenced by genetic polymorphism of IL-1 gene. Some studies report on an association between IL-1 and severity of periodontal disease genotype. [11] In a meta-analysis, it is demonstrated that IL-1α and IL-1β genetic variation are significant contributors to chronic periodontitis.11

Interleukin (IL)-1 and tumor necrosis factor (TNF) represent proinflammatory cytokines that stimulate several a number of events which occur during periodontal disease. These include the induction of adhesion molecules and other mediators that facilitate and increase the inflammatory response, the stimulation of matrix metalloproteinase, and bone resorption. The activity of these cytokines coincides with the critical events that occur during periodontal disease, namely, loss of attachment and bone resorption. The use of antagonists to IL-1 and TNF in experimental periodontitis have demonstrated a cause-and-effect relationship between the activity of these cytokines and the spread of an inflammatory front to deeper areas in the connective tissue, loss of connective tissue attachment, osteoclast formation, and loss of alveolar bone. In addition, the loss of fibroblasts that occurs during infection with periodontal pathogens is, in part, mediated by TNF. Thus, much of the damage that occurs during periodontal tissue destruction can be attributed to IL-1 and TNF activity. This destruction may very well represent an overreaction of the host response to periodontal pathogens caused by excessive production of IL-1 and TNF.12



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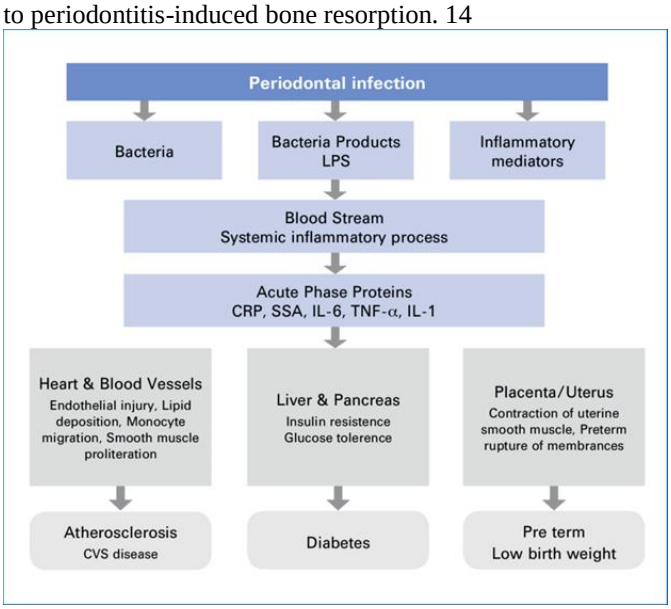
b) Interlukin – 6

Interleukin 6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene. In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Interleukin-6 (IL-6) is a molecule produced by different cells and tissues of the organism. It is involved in the production of acute phase proteins, proliferation of B-lymphocytes and neutrophils.

It has pro-inflammatory properties, plays a key role in acute inflammation, and promotes bone resorption. It also stimulates T-cell differentiation. [2] IL-6 is clearly an IL that mediates communication between a large number of cell types by playing a role in the proliferation and differentiation of B-lymphocytes, hematopoietic progenitors, hepatocytes, and T-lymphocytes. [3] IL-6 is also one of the cytokines found in gingival crevicular fluid (GCF) of patients with refractory periodontitis, who are undergoing active bone loss. [12] In this way, IL-6 which is a pro-inflammatory cytokine contributed to periodontitis-induced bone resorption. 14



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Prostaglandin

Proinflammatory cytokines, such as prostaglandin E2 (PGE2), interleukin (IL)-1beta, IL-6, and tumor necrosis factor-alpha are released from cells of the junctional epithelium, connective tissue fibroblasts, macrophages, and polymorphonuclear leukocytes. Enzymes, such as matrix metalloproteinase (MMP)-8, MMP-9, and MMP-13, produced by polymorphonuclear leukocytes and osteoclasts, all lead to the degradation of connective tissue collagen and alveolar bone. Studies have shown that PGE2 acts as a potent vasodilator and increases capillary permeability, which elicits clinical signs of redness and edema. It also stimulates fibroblasts and osteoclasts to increase the production of MMPs.15

Markers of alveolar bone loss

Many different biomarkers associated with bone formation, resorption, and turnover, such as alkaline phosphatase, osteocalcin, osteonectin, and collagen telopeptidases, have been found in GCF and saliva.[47] These mediators are associated with local bone resorption as well as with systemic conditions.

Systemic markers

C-reactive protein is produced by the liver and is stimulated by circulating cytokines, such as tumor necrosis factor-alpha and interleukin-1, from local and/or systemic inflammation such as periodontal inflammation. Circulating C-reactive protein may reach saliva via GCF or the salivary glands. High levels of C-reactive protein have been associated with chronic and aggressive periodontal diseases and with other inflammatory biomarkers.[19] C-reactive protein has recently been shown to be measurable in saliva from periodontal patients using a lab-on-a-chip method.[3]

Conclusion

Salivary levels of cytokines, TNF and IL-1β appear to serve as biomarkers of periodontitis. In periodontitis, microbial pathogens increase inflammatory infiltrate, that is, T-cells, B-cells, macrophages, and neutrophils with concomitant increase in inflammatory cytokines like IL-1, IL-11, IL-6, TNF-β, TNF-α, TGF-β, kinins, and thrombin [7]. In chronic inflammation, proinflammatory cytokines like IL-1, TNF-γ, IFN-α, and IL-6 play significant role in bone resorption by activating osteoclasts [8–10].

Interleukin-17 (IL-17) is a proinflammatory cytokine secreted by Th-17 cells. It is a powerful activator of neutrophils as it regulates G-CSF and its receptor and chemokine expression [11]. It contributes in the pathogenesis of various autoimmune and inflammatory diseases [12, 13]. It regulates antimicrobial activity of molecules like calgranulins, β-defensins, and mucin [11]. Its increased level has been documented in CP [14, 15]. Although periodontal infection (P. gingivalis) induces IL-17, the protective role of IL-17 against bone destruction has also been suggested [12, 16].

IL-6 is produced by many cells in response to LPS and it has both proinflammatory and anti-inflammatory roles. It is involved in inflammatory, regenerative, metabolic, and neural processes [17]. In CP, increased level of IL-6 in gingival crevicular fluid [18] and its significant reduction in serum after nonsurgical treatment of CP has been reported [19]. However, no significant differences in the levels of various cytokines in saliva of CP patients and healthy individuals were suggested [20].

In CP, most of the studies have investigated level of cytokines in serum or gingival crevicular fluid. The current study was designed to determine level of IL-6 and IL-17 in the saliva of patients with calculus associated CP.7

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