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Research Article

SALIVARY BIOMARKERS OF PERIODONTAL DISEASE- THE ULTIMATE DIAGNOSTIC TOOL

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ABSTRACT

Periodontitis is an inflammatory disease affecting the connective tissue attachment and supporting bone around the teeth whose initiation and progression are dependent on the presence of virulent microorganisms capable of causing the disease and the host response to pathogenic infection. In today's clinical practice, the current clinical diagnostics parameters like bleeding on probing, pocket depth, bone loss, gingival inflammation and plaque index measure disease severity rather than measuring disease activity and fails to identify the highly susceptible individuals who are at risk for disease progression. With the evolution of biomarkers, these limitations have been overcome. Various biological media like saliva, GCF are used to determine biomarkers in periodontal health and disease. This article presents an overview of the value of saliva as a reliable diagnostic tool and the role of various salivary biomarkers in physiological and pathological conditions with emphasis on its association with periodontal disease.

INTRODUCTION

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or a group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth formation, gingival recession or both. Advances in oral and periodontal disease diagnostic research are moving towards methods whereby the periodontal risk can be identified and quantified by objective measures such as biomarkers. According to National Institute of Health (NIH) "*biomarker*" refers to measurable and quantifiable biological parameters that can serve as indicators for health and physiological related assessments such as pathological process, environmental exposure, disease diagnosis and prognosis or pharmacological responses to a therapeutic intervention.[1,2,3] They are tell-tale molecules used to monitor the health status, disease onset, treatment response and outcome [4,3] and are used for screening and predicting the early-onset of the disease (prognostic tests) and evaluating the disease activity and efficacy of therapy (diagnostic tests). There are three types of biomarkers. i. A *predisposition biomarker* reflects the sensitivity of a subject to a disease.[5]ii.A *prognostic biomarker* predicts whether a subject will be susceptible to the disorder. iii. A *diagnostic biomarker* measures the incidence and progression of a disease process. Biological samples used for the detection of biomarkers in periodontal health and disease are saliva, GCF, serum and mucosal transudate.[6]

Ideal Requisites of A Biomarker: The ideal characteristics of a biomarker are: a**.** Ability to discriminate the progressive periodontitis from normal biological process and to detect the disease at an early stage and initiate preventive pretreatment and conduct epidemiological studies. b. Ability to classify the different forms of periodontitis c.Ability to identify the suspicious teeth d. Ability to affect the treatment planning e. Ability to monitor the treatment. f. Ability to demonstrate the distinct biological phases of periodontal disease.

Saliva As A Source of Biomarker For Periodontal Disease: Saliva is an important biological fluid that contains both local and systemically derived biochemical substances (serum-derived components, mediators of inflammation, collagen breakdown products), used for detecting periodontal disorders. In terms of periodontal diagnosis, whole saliva has elements that reflect the activity of all periodontal sites and therefore provide an indication of disease status in the mouth as a whole, in contrast to the site-specific GCF analysis. Hence, the determination of biomarkers in saliva is becoming an

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indispensable part of laboratory diagnostics and in the prediction of periodontal and other diseases.[7]

cathepsin-B are elevated in subjects with periodontal disease but lower in patients with gingivitis.[9]

Table 1 Salivary biomarkers to detect periodontal disease

Host derived enzymes & tissue breakdown products	Pro-inflammatory cytokines	Enzymes	Adipokines
Alkaline phosphatase	Prostaglandin E_2	Aspartateaminotransferase (AST)	Visfatin
Acid phosphatase	Interferon-γ	Lactate dehydrogenase	Chemerin
└,β-glucosidase	TNF-└	Myeloperoxidase(MPO)	Progranulin
β-glucuronidase	MMP-2,8,9	Lactoferrin, Lysozyme, Mucin	Resistin
Cathepsin-B	MMP-2,-3,-13,-7	Nitric oxide radical (NO)	
Elastase,Esterase	MIP -1└, 1β.	Dipeptidyl Peptidase-IV	
Fibronectin	IL-4,10,32,17A,18,6,1β	Alanine Aminopeptidase	
Arginase,Chitinase		Creatinine Kinase	
Bone specific biomarkers	**Markers of oxidative stress**	**Microbial markers**	**Non-enzymatic proteins and Immunoglobulins**
Osteopontin	8-hydroxydeoxyguanosine(80MdG)	P.gingivalis	Fibronectin, Albumin
Osteocalcin		A.actinomycetumcomitans, others	Cystatins, Neopterin
Osteonectin			C- Reactive Protein
Calprotectin			Histatins, IgA, IgM

Growth Factors	Metabolites	Others
Bone morphogenetic protein (BMP)	Dipeptides	Cortisol
Colony stimulating factor (M-CSF, G-CSF, GM-CSF)	Leucylisoleucine	Calcium
Epidermal growth factor (EGF)	Phenylphenol	Melatonin
Ephrins, Erythropoietin	Serylisoleucine	Volatile sulphur compounds
Fibroblast growth factor (FGF)(1-23)	Fatty acids like arachidonate, archidate,	
Hepatocyte growth factor (HGF)	dihomo-linodate, ionosine, lysine,	**Reactive O_2 species**
Insulin-like growth factor (IGF-1, 2)	putrescine, xanthine	
Neurotrophins, Thrombopoietin		Nitric Oxide radical
Placental growth factor (PAF)		
Platelet derived growth factor (PDGF)		
Transforming growth factor (TGF-└, TGF-β)		
Vascular endothelial growth factor (VEGF)		

Host Derived Enzymes and Tissue Breakdown Products

Alkaline Phosphatase: Alkaline phosphatase is used as a biomarker to determine the periodontal tissue damage, which is useful in diagnosis, prognosis and evaluation of post-therapy effects in periodontal disease[8] Kumar *et al* (2014) suggested that the salivary ALP can be used as a reliable marker for monitoring periodontal disease.[9]

ACID Phosphatase: In advanced stages of periodontal disease, the increased activity of AP is a consequence of destructive process in the alveolar bone and a decrease in the activity of this enzyme after periodontal therapy is a result of periodontal tissue repair.[10]

ALPHA Glucosidase: Sites with progressive clinical attachment loss demonstrate marked elevation in α glucosidase levels in salivary samples.

BETA Glucosidase: β-glucosidase is an important proteomic marker in saliva of chronic periodontitis subjects and is associated with severity of periodontal disease.[9]

BETA Glucuronidase*:* The salivary activity of βG increases proportionally with the severity of periodontal destruction.[11] Analysis of βG in saliva is a good diagnostic marker of periodontal disease[12]. Ginwalla *et al* (1972) found a significant association exists between periodontal clinical parameters (probing depth) & salivary β-glucuronidase.[11]

Cathepsin-B: Cathepsin-B is a vital marker that distinguishes periodontitis from gingivitis and in planning and monitoring treatment outcomes.[9] Ichimaru *et al* showed a positive correlation between cathepsin-B and severity of periodontal disease. Moreover, (Kinney *et al* 2007) GCF concentrations of

Elastase: Neutrophil elastaseis a vital marker of active periodontal tissue destruction.[13]. Eley and Cox demonstrated a positive correlation between elastase activity and clinical attachment loss.[14]

Esterase: Esterase's activity in whole saliva is higher in individuals with periodontal disease. The efficacy of periodontal treatment is monitored by the changes in levels of activity of esterase in whole saliva.[15]A significant positive correlation exists between the salivary esterase and calculus formation.[9]

Fibronectin: In periodontitis, a decrease in the level of fibronectin in saliva is evident. Fibronectin blocks adhesins of many periodontal microorganisms, reducing their adherence to periodontal tissues.[16] P. gingivalis fimbriae bind to salivary fibronectin in periodontitis as a result, salivary fibronectin is reduced in periodontitis.[14]

Arginase: In periodontitis, there is an increase in salivary arginase activity causing a decrease in NO synthesis, also leads to a decrease in the antibacterial property of saliva and cause periodontal tissues to become more susceptible to existing pathogens.[12] Ozmeric *et al* reported a significant variation in salivary arginase activity in periodontitis subjects.[9]

Chitinases: Van Steijn *et al* demonstrated an increase in the salivary chitinase activity in the saliva of periodontitis and their levels decreased following therapy.[14] Periodontal treatment for a period of 5-6 months resulted in a three to four fold decrease in this enzyme activity.[17]

PRO-Inflammatory Cytokines

Prostaglandin E_2: PGE_2 levels are increased with disease severity and decreased with therapy.[18] The salivary levels of PGE_2 distinguishes gingivitis from health and subjects with gingivitis who return to clinical health continue to produce inflammatory mediators for weeks following oral prophylaxis.[19]

Interferon-γ: Ribeiro *et al* demonstrated that the periodontal treatment decreases bleeding on probing and increases the level of IFN-γ, which is involved in immune responses and induces mainly cell mediated responses.[20]

Tumour Necrosis Factor-ᒪ: Salivary TNF-α levels are highest in CP than AP[28] and it has a link with the development of cardiovascular disease.[22] The severity of periodontitis is associated with local increase in TNF-α whereas inhibition of these substances produce substantial reduction in periodontal disease.[23] Subjects with salivary TNF-α levels above a threshold level of 5.75 pg/ml had significantly more sites with bleeding on probing.[21]

Interleukin-1β: Nakashima *et al* (2013) observed that IL-1β has effects on bone coupling process[25] whose levels are remarkably elevated in moderate and severe forms of periodontitis with disease severity and decreased following periodontal therapy.[18] A significant relationship exists between the IL-1β and clinical attachment level.[18]A positive correlation was observed between IL-1β and passive smoking.[27] Salivary IL-1β is considered to be a good diagnostic biomarker for discriminating between active and inactive periodontal sites.[16]

Interleukin-6 (IL-6) /B-CELL Stimulating Factor-2 (BSF-2): Interleukin-6 is a significant biomarker for the diagnosis of periodontal disease.[28]It is a powerful stimulator of fibroblast MMP secretion and is a key cytokine in the propagation of the inflammatory response to plaque bacteria.[24]Salivary levels of IL-6 distinguishes periodontal health from disease. [25] It is a reliable biomarker associated with alveolar bone loss.[29]

Matrix Metalloproteinase-2 (MMP-2)/Gelatinase-A: Rai *et al* (2008) observed that MMP-2 may serve as a biomarker of periodontal disease and aid in early detection of periodontitis and gingivitis.[30]

Matrix Metalloproteinase-8 (Collagenase-2): MMP-8 is the principal biomarker for assessing the periodontal disease activity reflecting the extent of periodontal disease and it helps to predict the future disease progression.[31,32] They are crucial biomarkers of GCG and AP.[33]There is a strong association between the salivary levels of MMP-8 with advanced periodontitis but smoking weakens the association.[34] MMP-8 is associated with bleeding on probing and number of deepened periodontal pockets.[35]

Matrix Metalloproteinase-9 (MMP-9)/Gelatinase-8: Salivary MMP-9 (matrixin) serve as biomarker of periodontal disease and aid in early detection of periodontitis or gingivitis.[30]

MMP-2,MMP-3,MMP-13,MMP-7: MMP-2 serves as a biomarker of periodontal disease and aid in early detection of periodontitis or gingivitis.[3]Ma *et al* found elevated levels of both MMP-13 (collagenase-3), MMP-8 correlated with irreversible peri-implant vertical bone loss around loosening dental implants.[36]. MMP-7 is a candidate biomarker of periodontal disease.[37]

Macrophage Inflammatory Protein-1ᒪ,1β (MIP-1ᒪ,1β): MIP-1α aids to understand the progress of alveolar bone loss in subjects with periodontitis.[38] It also helps to monitor the periodontal disease status and reflects its response to periodontal therapy.[32] Hence, MIP-1α is a significant biomarker for the diagnosis of periodontal disease.[39]

Interleukin-10 (IL-10): Periodontal treatment does not appear to affect salivary IL-10 concentrations.[40]

Interleukin-32 (IL-32): IL-32 is a principal biomarker linked with the progression and intensity of periodontitis and its presence in saliva, GCF acts as a valuable tool for identifying periodontal disease.[41]

Interleukin-17A (IL-17/IL-17A): IL-17A, IL-17E, IL-A/F ratio are used as a vital marker in the early diagnosis of periodontitis. Salivary levels of IL-17 is low in chronic periodontitis.[42]

Interleukin-18: IL-18 is a novel inflammatory marker associated with periodontitis and plays a role in the periodontal pathogenesis.[39] Therefore, IL-18 is a principal biomarker of periodontal tissue destruction and gingival inflammation.[42]

Enzymes

Aspartate Aminotransferase: A positive correlation is observed between the salivary levels of AST and passive smoking.[27]Cesco *et al* (2003) suggested that salivary AST is a candidate marker of periodontal disease and its levels correlated with periodontal pockets, gingival bleeding and suppuration.[43]

Lactate Dehydrogenase: Salivary LDH is a potential biomarker for evaluating the periodontal tissue damage[24] and aids in diagnosis, prognosis and evaluation of therapy effects.[44]

Myeloperoxidase: MPO is a vital biomarker of generalized chronic and aggressive periodontitis[33]. MPO is associated with periodontal tissue destruction.[45] It is a candidate biomarker for site-specific diagnosis of periodontitis.[46]

Lactoferrin: An elevated level of lactoferrin is observed in saliva of subjects with periodontitis & their levels decreased following periodontal therapy.[9] Ferreira *et al* (2015) suggested that lactoferrin is a potential marker in modulating inflammatory response in gingivitis and periodontitis.[47]

Lysozyme: Jalil *et al* found that patients with low levels of lysozyme in saliva are more susceptible to plaque accumulation, which is considered as a risk factor for periodontal disease[9]

Mucin: Lundmark *et al* stated that Mucin-4 is a candidate biomarker of periodontal disease.[37]

Nitric Oxide Radical (No): Ozmeric *et al* found that the increased salivary arginase activity in periodontitis perhaps causing a decrease in NO synthesis also leads to a decrease in the antibacterial property of saliva and cause periodontal tissues to become more susceptible to existing pathogens.[17]

Dipeptidyl Peptidase-IV: Ozmeric *et al* (2004) found that the levels of DPP-IV is increased in periodontitis.[17]

Alanine Aminopeptidase: Ozmeric *et al* concluded that the activity of AAP in whole saliva of subjects with periodontitis were elevated indicating it is an important marker of periodontitis[17]

Creatinine Kinase: Todorovic *et al* (2006) stated that salivary CK serve as biomarker of periodontal tissue damage and aid in the diagnosis, prognosis and evaluation of therapy effects.[44]

Adipokines

Visfatin: Tabari *et al* (2014) suggested that visfatin is a new candidate inflammatory biomarker whose levels in saliva are elevated in chronic periodontitis.[48]

Chemerin: Özcan *et al* (2015) reported that chemerin is a newly emerged candidate biomarker involved in the pathogenesis of periodontal disease.[49]Dogan *et al* (2016) demonstrated that the production of chemerin is elevated in periodontitis and Type-II DM and its levels are reduced following periodontal therapy, indicating that chemerin acts as a diagnostic and prognostic marker for efficiency of periodontal disease and DM therapies[50]

Progranulin: Progranulin serves as a marker of chronic inflammatory response in chronic periodontitis and Type-II DM.

Resistin: Mittal *et al* (2015) concluded that Resistin is a new biomarker that is used to diagnose as well as monitor inflammatory diseases and serves as a crucial marker for rheumatoid arthritis and periodontitis.[51]

Bone Specific Biomarkers

Osteopontin: Osteopontin serves as a possible biomarker of periodontal disease progression. There is a positive correlation between increased levels of OPN and probing pocket depth.[52]

Osteocalcin: Delmas *et al* stated that serum osteocalcin is presently a valid marker of bone turnover when resorption and formation are coupled and is a specific marker of bone formation when formation, resorption are uncoupled. McGehee *et al* (2004) found that osteocalcin is a valid salivary biomarker of bone turnover.[53]

Osteonectin: Kinney *et al* (2007) demonstrated that osteonectin is a more sensitive marker for detection of periodontal disease status.[7]Scannapieco *et al* (2007) found that osteonectin is a bone-specific salivary biomarker that predicts the future alveolar bone loss.[54] A positive correlation is observed between the osteonectin levels and the alveolar bone loss score (Patricia *et al* 2007).[29]

Calprotectin: In periodontal disease, calprotectin improves resistance to P.gingivalis by boosting the barrier protection and innate immune functions of the gingival epithelium.[7]

Markers of Oxidative Stress

8-Hydroxydeoxyguanosine (8-OHdG): Takane *et al* (2002) stated that 8-OHdG is a vital marker to evaluate oxidative damage and its levels in the saliva reflects the status of periodontal health.[55] Kurgan *et al* (2015) demonstrated that liquid chromatography with tandem mass spectrometry (LCMS/MS) is more reliable and sensitive method than ELISA to evaluate 8-OHdG levels to monitor the treatment response of periodontitis.[25]

Microbial Markers

Porphyromonas Gingivalis, Aggregatibacter Actinomycetumcomitans and Others: Socransky *et al* demonstrated that the red complex bacteria (P.gingivalis, T.denticola, T.forsythia) are highly implicated in the progression of periodontal disease. A.actinomycetumcomitans is an important etiological agent in the initiation of periodontal disease. Others include P.intermedia, T.denticola, T.forsythia, Fusobacterium nucleatum, Prevotella nigrensis, Campylobacter rectus, T.socranskii, peptostreptococcus, mycoplasma species. Salivary microflora serves as potential biomarkers for the diagnosis of periodontal disease.

Non-Enzymatic Proteins And Immunoglobulins

Fibronectin: In periodontitis, a decrease level of fibronectin in saliva is observed. P.gingivalis fimbriae binds to salivary fibronectin in periodontitis as a result, salivary fibronectin is reduced in periodontitis.

Albumin: Nishida *et al* (2006) found that albumin is a candidate marker of periodontal disease associated with passive smoking.[27]

Cystatins: Cystatin-C and Cystatin-S levels are elevated in saliva of subjects with periodontitis. ***Neopterin:*** In chronic periodontitis, elevated levels of neopterin are observed in saliva and serves as a potential biomarker for identification of periodontal disease in its initial stage.[9]

C-*Reactive Protein*: In periodontitis, salivary CRP levels increase.CRP is an important local as well as systemic inflammatory biomarker and its levels are elevated in chronic oral infections and coronary artery disease.[56]

Histatins: Patients with low levels of histatins in saliva are more susceptible to periodontitis, which is considered as a risk factor for periodontal disease.

Immunoglobulins-A (IgA), IgM: Seeman *et al* demonstrated that the patients with periodontal disease are shown to have higher salivary levels of IgA, IgG, IgM specific to periodontal pathogens compared with healthy subjects.

Growth Factors: Growth factors like Bone morphogenetic protein (BMP), Colony stimulating factor (M-CSF, G-CSF, GM-CSF), Epidermal growth factor (EGF), Ephrins, Erythropoietin, Fibroblast growth factor (FGF)(1-23), Hepatocyte growth factor (HGF), Insulin-like growth factor (IGF-1, 2), Neurotrophins, Placental growth factor (PAF), Platelet derived growth factor (PDGF), Thrombopoietin, Transforming growth factor (TGF-α, TGF-β), Vascular endothelial growth factor (VEGF). Scannapeico *et al* (2007) found that salivary hepatocyte growth factor serve as a biomarker to predict the future alveolar bone loss.[54] Jaedicke *et al* (2016) concluded that hepatocyte growth factor is a robust marker for periodontal disease.[57]

Metabolites

In periodontal disease, increase levels of fatty acids, dipeptides, monosaccharides are noted. Certain metabolites like dipeptides, leucylisoleucine, phenylphenol, serylisoleucine, fatty acids like arachidonate, archidate, dihomo-linodae, ionosine, lysine, putrescine, xanthine are the important salivary biomarkers of periodontal disease. Salivary metabolomics analyses the

metabolic profile of saliva to establish a definite diagnosis and monitor the periodontal disease (Mikkonen *et al* 2016).[58]

Others

Cortisol, Calcium, Melatonin: Genc *et al* reported high levels of salivary cortisol in subjects with severe periodontitis. Calcium ion is the most extensively studied as a periodontal marker for periodontal disease in saliva. Almughrabi *et al* (2013) demonstrated that the levels of melatonin in GCF and saliva are decreased in periodontitis and higher in healthy subjects.[59]

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