



## Review Article

## Salivary diagnostic biomarker for periodontal disease - A review

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## ABSTRACT

Periodontitis is chronic inflammation of the periodontium caused by persistent bacterial infection affecting the connective tissue attachment and supporting bone around the teeth. As the ability to reconstruct the periodontium is limited after alveolar bone loss, early diagnosis and intervention should be paramount goals of periodontal treatment preventing future disease's progression. Saliva is a physiologic fluid that contains complex mixture of substances as well as inflammatory biomarkers associated with periodontitis. Conventional clinical criteria are often insufficient for determining sites of active disease, for monitoring the response to therapy, or for measuring the degree of susceptibility to future disease progression. Therefore, the use of saliva has provided a substantial addition to the diagnostic armamentarium as an investigative tool for disease processes. With the current technological advances, together with point-of-care detection systems, salivary analysis will be valued much more highly in the near future. Even though saliva is easy to manipulate with low-cost storage, careful attention must be directed to limit variation in specimen integrity. This review focuses on the biomarkers in saliva that appears to be promising in the future for periodontal diagnosis, as well as some contemporary diagnostic tests available.

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## 1. Introduction

Periodontitis is a chronic, site-specific, polymicrobial disease of multifactorial etiology which is complicated by both environmental and genetic factors.<sup>1</sup> It is initiated as a response to the dental plaque on the tooth surface adjacent to the gingival margin followed by inflammation leading to dysbiotic environment of the oral ecosystem characterized by tissue destruction and quiescence, similar to many other chronic illnesses.<sup>2,3</sup>

Clinical parameters like probing depth, bleeding on probing, plaque index, attachment level and radiographic features of alveolar bone loss indicates the retrospective evidence of periodontitis but do not measure present disease activity, while microbiological tests, host response analysis, and genetic analyses have been suggested to control this

problem.<sup>4</sup> The majority of the parameters used to determine periodontal disease diagnosis and prognosis are tooth-related rather than subject-related. Therefore, searching for indicators as per the patient level might be favourable for monitoring health.<sup>4</sup> Thus, saliva should include biomarkers specific to the physiological elements of periodontitis, and changes within the components of these biomarkers might have diagnostic implications.<sup>5,6</sup>

Saliva, an oral biofluid produced by the major and minor salivary glands, has critical physiological and host defence functions against the microbial attacks from the dental biofilm. Their physicochemical properties, along with its composition, has different functions including antibacterial, antiviral and antifungal, buffering capacity, protection and repair of hard tissues, lubricating and defensive actions to the gingival tissues. Saliva contains local and systemic indicators, implying that saliva might be useful tool

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for diagnosis of periodontal disease.<sup>7</sup> In addition, using disease-specific biomarkers enhances the specificity and sensitivity of diagnostic and prognostic data.<sup>7,8</sup> There are various inflammatory biomarkers that can be discovered in saliva which is constantly associated with periodontitis.<sup>6</sup>

### 1.1. Collection of Saliva

Saliva that is collected for diagnostic purpose includes:

1. Expectorated whole saliva.
2. Samples derived from the specific salivary glands.
3. Minor salivary glands and gingival crevicular fluid.

It can be stimulated (mechanical stimulation of saliva secretion) or unstimulated (resting saliva). Patients should refrain from eating, drinking, and plaque control measures 1 hr before collecting whole saliva while chewing gums, hard plastic, paraffin, citric acids or pharmacologic agents can be used for stimuli for the rapid secretion for assessing stimulated saliva.<sup>9</sup>

Individual gland secretions are favoured, and this may be performed non-invasively utilising appropriate collection equipment. Plastic adaptations of a single cup, initially produced in 1910 by Carlson and Crittenden, are preferred for collecting parotid saliva.<sup>10</sup> For this reason, disposable and personalised collectors have now been created. Saliva from the sub-mandibular and sub-lingual region can also be collected using aspiration from the duct apertures by micropipettes or using a customised plastic collector.<sup>9</sup>

## 2. Biomarkers

A biomarker is a substance that can be quantitatively measured and assessed as an indicator of a biological state of a physiological as well as a pathological process or pharmacological response to a therapeutic intervention."<sup>11</sup> For the purpose of diagnostic, staging, and prognosis of a certain disease, biomarker act as a trustworthy method to determine the biological process.<sup>12</sup> Thus, periodontitis markers should have the following characteristics.<sup>1</sup>

### 2.1. Clinical application

Salivary diagnostics is an attractive biofluid because of following features:<sup>13</sup>

1. Easy to collect in a non-invasive manner.
2. Does not need trained medical personnel.
3. Repetitive samples can be taken for follow-up purposes.
4. Unlike blood samples, it significantly reduces pain and anxiety.
5. Samples are easier to ship and store.
6. Saliva handling is minimally technique sensitive with no potential for cross-contamination.

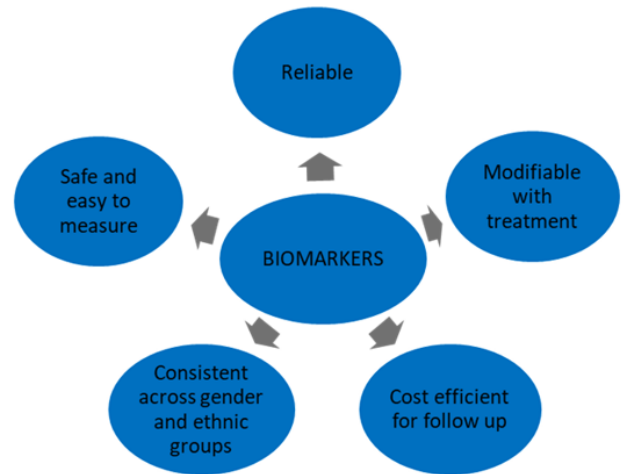


Fig. 1: Criterion for ideal Biomarker

7. Its cost-effectiveness allowing a broad screening strategy to enhance public health screening for larger populations.

Salivary diagnostics has developed recently as a point-of-care devices for sensing biomarkers non-invasively in dental offices that allows measurement of even small volume (microliters) of whole saliva in real time.<sup>14</sup> Furthermore, it can be utilised for the multiplex measurement of three salivary biomarkers; C-reactive protein, MMP-8, and IL-1b levels, which are related to periodontitis.<sup>15</sup> A point-of-care device could give dentists the means to heighten patients' compliance by giving patients quick feedback about treatment effects.<sup>14</sup>

### 2.2. Salivary biomarkers of periodontal disease<sup>2</sup>

Table 1: Salivary biomarker of periodontal disease

Specific Markers	Nonspecific markers	Inflammatory markers	Other markers
Immunoglobulins	Lactoferrin	Alkaline phosphatase	C-reactive protein
Salivary enzymes and ions	Mucins	Osteonectin	Oxidative stress marker
	Histatin	Osteocalcin	
	Fibronectin	Collagenases (MMP-1, -8, -13)	
	Cystatins	Gelatinases (MMP-2, -9)	
	Platelet-activating factor	Tissue inhibitors of MMPs, TIMP-1	
	Growth factors & hormones		

### 2.3. Specific Salivary Biomarkers of Periodontal Disease

Immunoglobulins (Ig) are the polypeptide chains with two light and two heavy chains that are produced by plasma cells and lymphocyte having a vital role in defence mechanisms. Immunoglobulins (IgA, IgG, and IgM) have an impact on oral microbiota as they hinder in adherence and bacterial metabolism.<sup>16</sup> (IgA) is predominant in secretions including tears, saliva, and milk which also provides neonates with protection against intestinal infections.<sup>17</sup> Specific immunoglobulins present in saliva directed against periodontal infections have also been studied for their diagnostic values. IgG concentration in saliva rises followed by inflammation in the periodontal tissues along with increased vascular permeability and flow of GCF.<sup>17</sup> Guven et al.<sup>18</sup> reported that patients with gingivitis and periodontitis had higher levels of IgA in whole saliva in comparison to healthy controls, showing the positive correlation between IgA concentration and the degrees of inflammation. Sandholm et al.<sup>19</sup> evaluated salivary IgA, IgG, and IgM in the whole saliva collected from 21 patients with aggressive periodontitis and found out higher levels of salivary (IgA, IgG and IgM) levels to *A. actinomycetemcomitans* in the saliva of patients.

Lysozyme is a specific protein with antimicrobial properties acting on both gram positive and gram negative bacterial cell wall peptidoglycan. It can cause lysis of few bacterial species by hydrolysing glycosidic linkages present in the connections in bacteria's cell. Patients with systemic disease and plaque accumulation will have low salivary lysozyme levels as compared to healthy individuals.<sup>20</sup>

Calcium (Ca) is a ion which is detected in high numbers in whole stimulated saliva as a marker for periodontal disease. Nevertheless, Ca has limited importance as a indicator for periodontal disease as relationship between them is not well-defined.<sup>21</sup>

### 2.4. Nonspecific Salivary Biomarkers of Periodontal Disease

Lactoferrin inhibits microbial growth by absorbing iron from the environment and leaving the bacteria without iron. It is secreted by salivary glands, which is upregulated during gingival inflammation. In case of periodontitis, adequate iron is not available so it degrades into products that can damage tissue.<sup>22,23</sup>

Mucins are the lubricating proteins, released by mucous cells in the submandibular, sublingual, palatine, and labial salivary glands. Mucins gets concentrated at the boundary of the oral mucosa and the outer environment, shaping a self-protective layer against drying up and environmental challenge.<sup>2,24</sup> The mucin interacts with *A. actinomycetemcomitans*, thus, decreases their pathogenic potential through its antibacterial actions.<sup>24</sup>

Fibronectin is a protein of extracellular matrix that encourages cell adhesion, growth, differentiation and migration of an organisms. It stops bleeding and guards the underlying tissue as well as plays a key role in inflammation, wound healing and repair of the tissues. Histatin is a salivary protein with antimicrobial properties secreted from parotid and submandibular glands effective in inhibiting bacterial and host enzymes involved in periodontitis.<sup>25,26</sup>

Cystatins are proteolytic enzymes found mainly in the tissues, bodily fluids and the saliva, derived from pathogenic bacteria, inflammatory cells, fibroblasts and osteoclasts. Cystatins can cause tissue destruction by exerting its collagenolytic property. These enzymes in the saliva are mainly derived from the submandibular and sublingual salivary glands, and minimum amount from the parotid gland.<sup>27</sup>

Platelet activating factor (PAF) is an endogenous phospholipids which is an effective mediator of inflammation that affects smooth muscle contraction, vascular permeability and inflammatory cell stimulation. Garito et al.<sup>28</sup> found a positive relationship between Platelet activating factor and periodontal inflammation.

Epidermal growth factor (EGF) is polypeptide synthesized by a range of normal cell types, and human. EGF displays numerous biologic capabilities, including stimulation of proliferation and differentiation of epithelium and mesenchyme-derived tissues; stimulation of DNA, mRNA, protein, and hyaluronic acid synthesis; and anti-apoptosis.<sup>7</sup> In addition, EGF can stimulate cell migration and proteinase production and accelerate epithelial regeneration and wound healing.<sup>29</sup>

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a component of whole saliva with angiogenic potential that stimulates formation of blood vessels thus, aiding in inflammation and wound healing. Periodontitis patients showed high concentration of VEGF in whole saliva.<sup>29</sup>

Salivary leukocytes enters the oral cavity via the gingival crevice. Klink hammer et al.<sup>30</sup> standardized collections and counting of leukocytes in saliva and also developed the orogranulocytic migratory rate (OMR) which can be used as a laboratory test. It seemed that saliva could serve as a growth medium for oral *Streptococcus* species and *Actinomyces*. viscous. Nomura et al.<sup>31</sup> quantitatively estimated the salivary periopathogens in patients with treated periodontitis and progressive periodontitis and reported statistically significant increment in *P. gingivalis* and *P. intermedia* levels in the progressive periodontitis group.

## 3. Inflammatory Markers

Many biomarkers associated with bone formation, resorption, and turnover, such as cytokines, alkaline phosphatase, osteocalcin, osteonectin, and collagen

telopeptidases, have been evaluated in GCF and saliva.<sup>32-34</sup> These mediators are associated with local bone metabolism as well as with systemic conditions.

Matrix metalloproteinases (MMP) are the family of endoproteinases that is responsible for both tissue degradation and remodeling. Gingival and periodontal ligament collagens are destroyed by host cell-derived interstitial collagenases during progressive periodontal breakdown. MMP-8, also referred as collagenase-2 is the dominantly found in diseased periodontal tissue and GCF. Using a rapid point-of-care microfluidic device, the level of MMP-8 was demonstrated to be highly increased in saliva from patients with periodontal disease.<sup>32</sup> Moreover, after periodontal treatment significant changes in salivary MMP-8 was reported suggesting their potential to predict the risk of future disease occurrence and to monitor treatment interventions.<sup>32</sup>

Gelatinase (MMP-9)/Type IV collagenase, produced by neutrophils, macrophages and fibroblasts which degrades the collagen intercellular ground substance including type 4 collagen. It is activated by Cathepsin G and inhibited by tissue inhibitor of metalloproteinases (TIMP-1). This biomarker has been constantly reported increased salivary levels in the clinically healthy and diseased state. Teng et al.<sup>33</sup> found a twofold increase in the mean MMP-9 levels in patients with increase in attachment loss. Considering these results, future use of MMP-9 in salivary diagnostics may serve as a guide in periodontal treatment monitoring.

Collagenase-3(MMP-13), has a specificity towards interstitial collagen type I,II,III,IV and gelatin. MMP-13 may one day be utilized to analyze and follow the movement of periodontal sickness, just as to gauge the achievement of therapy.<sup>34</sup>

Alkaline Phosphatase (ALP) is host-derived enzyme active at alkaline pH, present intracellularly particularly in the bones that is involved in the maintenance of periodontal ligament and root cementum. High ALP activity are indicative of alveolar bone destruction due to periodontitis, which establishes this enzyme as potential salivary biomarker for periodontitis.<sup>35-37</sup>

Osteopontin is a single-chain polypeptide having a molecular weight of approximately 33 kDa. Osteopontin is concentrated more in attachment areas of the plasma membrane in bone matrix. It binds with hydroxyapatite and encodes the protein that is involved in the attachment of osteoclasts to the mineralized bone matrix. A study by Sharma CD et al<sup>38</sup> showed high osteopontin levels in saliva with the progression of periodontal disease which was significantly reduced when nonsurgical periodontal treatment was provided.

### 3.1. Other Markers

Circulating C-reactive protein (CRP) is the component of innate immune system released in response to inflammation.

Mostly, CRP is generated by hepatocytes in the liver induced chiefly by Interleukin-6 (IL-6), IL-1 $\beta$  and TNF (4). Even though majority of CRP are produced from the liver, CRP and IL-6 mRNAs have been discovered in gingival tissue samples or the salivary glands from periodontitis patients.<sup>39</sup>

Oxidative pressure is described as an imbalance between oxidant and defensive factors due to excess of oxygen-derived free radicals or a decline in antioxidant systems.<sup>40-42</sup> Kim et al<sup>40</sup> reported rise in amount and activity of antioxidants in saliva after scaling.

8-hydroxydeoxyguanosine (8-OHdG) is the major products liberated by bodily fluids as a response to oxidative damage to DNA. Increased levels of salivary 8-OHdG and low levels of saliva antioxidants expressed increased oxygen radical activity.<sup>34,42</sup> Hendek MK et al.<sup>43</sup> have assessed that the mean 8-OHdG level in saliva quantified pathogens associated with periodontitis and showed to be a beneficial biomarker for evaluating periodontal status and efficacy of periodontal treatment.

### 3.2. Future Prospects of Periodontal Diseases Using Saliva

A large sort of biomarkers for periodontal disease have been found but none of them has been widely used in clinical practice.<sup>6,25</sup> This is mostly due to the lack of a well-established technology for measuring salivary contents in real-time within a dental chair, which might make salivary diagnostics a highly great tool for dentists.<sup>25</sup>

Major challenges in diagnosing periodontal disease using saliva are<sup>44</sup>

1. Markers of the inflammations are not disease specific and are based on general microbial and inflammatory cytokines.
2. Complexity of the microflora and host response to limit bacterial challenge, it is difficult in defining specific biomarkers for periodontal disease.

In order for the salivary diagnostics for periodontal diseases to be clinically relevant, the acceptable bioinformatics should be augmented so that validated biomarkers have disease discriminatory power. Biomarkers should not only diagnose the disease but also predict the future risk of disease activity by simple means.<sup>44</sup>

Point-of-care salivary technologies are being developed, that assists biomarker identification without laboratory procedures and can be performed yet at the patient's home, or the dental clinics. These self-performed non-invasive diagnostic testing such as Oral Fluid NanoSensor Test (OFNASET) for detection of salivary proteins as well as oral cancer, My PerioId for detection of genetic susceptibility of periodontal disease, OraRisk HPV test (OralDNA Labs) to detect oral human papillomavirus (HPV) infection,

Oraquick for HIV infection assist in clinical decision-making and helps to monitor the periodontal disease progression.<sup>14,45</sup>

Recently, salivary diagnostics is based on development of microfluidics or micro/nanoelectromechanical systems (MEMS/NEMS) consisting of electrical, mechanical, and functional elements such as sensors, actuators, and microelectronics which permit to measure proteins, DNA, transcripts (mRNA), electrolytes, and small molecules present in the saliva.<sup>46</sup> These modern tools also includes electrochemical sensing, lab-on-chip, RT-PCR, fibre optic microsphere-based arrays, high-throughput DNA microarrays, resonance-based fiber optic sensors, and microchip-based electrophoretic immunoassay.<sup>45,46</sup>

The new possibility of point-of-care diagnostics for “lab-on-a-chip” enables the detection of multiple biomarkers, and thus simultaneous diagnosis of many diseases. It seeks to integrate and automate all the complexities of a laboratory procedure into a device of the size of a computer chip.<sup>15</sup> Directions should also include continuous investigations to evaluate complex disease signatures to enable for accurate chair-side diagnosis and improved customized therapy.<sup>47</sup>

#### 4. Conclusions

Periodontal disease is a multifaceted, complicated disease, and though many periodontitis-related biomarkers have been identified, only a handful have been thoroughly examined in suitable longitudinal research. Still, challenges remain ahead for identifying highly specific and sensitive biomarkers for evaluating existing and future destructive periodontal disease activity.

Probing, visual examinations, and radiography are still used to diagnose periodontal disease today, despite the fact that they were first used more than half a century ago. When it comes to exact illness categorization, these methods are often suboptimal for disease classification, therapeutic planning, and prognosis. Salivary biomarkers provide additional information to both clinician and patient regarding present state and heightened risk for future disease activity. Saliva has gained popularity for diagnostic purposes greatly due to its highly enriched content of disease biomarkers, its easy availability and non-invasive methods of collection.

Current advances in salivary analytic innovation along with point-of-care biosensor technologies undoubtedly give reason to hypothesize that saliva might eventually be the bio medium of choice for the diagnosis in clinical diagnostics. This would be an important step in enhancing personalized medicine allowing every patient the optimal treatment as well as identifying refractory or progressive cases. A practical, easy to-utilize point-of-care analysis that just requires a solitary drop of salivation which would impact worldwide medical care.

#### 5. Conflicts of Interest

All contributing authors declare no conflicts of interest.

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None.

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