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Salivary Biomarkers: A Noninvasive Revolution In Periodontal Disease Diagnosis

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Abstract

Early detection of periodontal disease is critical for effective treatment and preventing complications. In recent years, salivary biomarkers have emerged as valuable tools for diagnosing and monitoring periodontal diseases, offering a noninvasive and easily accessible diagnostic medium. Periodontal disease is a chronic inflammatory condition affecting the supporting structures of teeth, and traditional diagnostic methods, such as clinical and radiographic assessments, provide limited information about disease activity and future risk. Saliva, however, contains a rich array of biomarkers, including immunological, enzymatic, microbial, and inflammatory markers, which can reflect both oral and systemic health. This review explores the role of salivary biomarkers, including specific markers like immunoglobulins, enzymes, and cytokines, in assessing periodontal disease. It also discusses the potential of emerging technologies, such as microfluidic devices, in improving the diagnostic utility of saliva for periodontal health. Despite some challenges, the growing interest in saliva as a diagnostic tool holds promise for more precise and personalized periodontal care.

Keywords: Salivary biomarkers, periodontal disease, diagnostic tool, noninvasive diagnostics, periodontal health

Introduction

Salivary biomarkers have emerged as a promising tool in periodontics, offering a non-invasive, efficient, and potentially more accurate method for diagnosing and monitoring periodontal diseases. These biomarkers, found in saliva, can reflect the presence, risk, and progression of periodontal disease, providing valuable insights into disease activity and treatment efficacy. [1] Salivary biomarkers offer a non-invasive alternative to traditional diagnostic methods, which often rely on clinical assessments and radiographic imaging. These biomarkers can provide early detection of periodontal diseases, which is crucial for effective treatment and management.[1-3] Microbial and inflammatory biomarkers in saliva, such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, IL-1β, and MMP-8, have shown potential as accurate indicators of periodontal disease and treatment outcomes. These biomarkers can objectively measure periodontal risk and disease progression.[3,4]
The salivary microbiome, analyzed through advanced sequencing techniques, has demonstrated potential as a diagnostic tool for periodontitis. Studies have shown that specific microbial profiles in saliva can distinguish between healthy and diseased states with high sensitivity and specificity[5] Salivary biomarkers can be used to monitor the effectiveness of periodontal treatments. For instance, non-surgical periodontal therapy has been shown to significantly reduce levels of inflammatory biomarkers such as IL-1β, IL-6, and MMP-8 in saliva, reflecting clinical improvements[3,6] The salivary proteome, which includes a wide array of proteins, can provide insights into the biological processes underlying periodontal disease and response to treatment. Changes in protein expression post-treatment can serve as prognostic indicators.[7]Salivary biomarkers can also correlate with systemic conditions, such as coronary heart disease, highlighting their potential role in assessing overall health and disease interactions.[4]
While salivary biomarkers hold great promise in periodontics, there are challenges to be addressed, such as the variability of analyte levels and the need for standardized protocols. Additionally, the integration of these biomarkers into clinical practice requires further validation and development of predictive algorithms to enhance their diagnostic and prognostic utility. This overview explores the role of salivary biomarkers in periodontics, highlighting their diagnostic and prognostic capabilities, and the potential they hold for revolutionizing periodontal care.

Need for Salivary Biomarker for Periodontitis

The need for salivary biomarkers in diagnosing and managing periodontal disease is increasingly recognized due to the limitations of traditional clinical assessments. These biomarkers offer a non-invasive, accessible, and potentially more accurate method for early detection, monitoring disease progression, and evaluating treatment efficacy. Salivary biomarkers can provide insights into both microbial and inflammatory aspects of periodontal disease, making them valuable tools in modern dentistry.

Non-Invasive and Accessible: Saliva collection is simple, non-invasive, and can be performed without specialized equipment, making it an ideal medium for regular monitoring and early detection of periodontal disease. [2,8]
Comprehensive Diagnostic Potential: Salivary biomarkers can reflect the current status of periodontal disease and predict its progression and response to treatment. They encompass a range of biological markers, including enzymes, proteins, and genetic material, which can provide a holistic view of the disease.[9,10]
Correlation with Clinical Parameters: Studies have shown that salivary biomarkers can correlate with traditional clinical parameters, such as probing depth and attachment level, offering a more comprehensive assessment of disease severity and activity.[11]

Types of Salivary Biomarkers
Specific Biomarker: Immunoglobulins, particularly secretory IgA (sIgA), play a crucial role in the defense mechanisms of saliva, influencing oral microbiota by interfering with bacterial adherence and metabolism. sIgA is predominantly found in saliva, along with smaller amounts of IgG and IgM. Research shows a positive correlation between higher sIgA levels and the severity of periodontal inflammation. Studies also suggest elevated levels of IgA and IgG in the saliva of periodontitis patients, especially against pathogens like Porphyromonas gingivalis, Treponema denticola, and Aggregatibacter actinomycetemcomitans. [3,5]
Inflammatory Biomarkers: Inflammatory markers like interleukin-1β (IL-1β) and matrix metalloproteinase-8 (MMP-8) are widely used for diagnosing periodontitis and predicting treatment outcomes. These markers can indicate the presence and severity of inflammation in periodontal tissues.[3,12]
Proteomic and Genomic Biomarkers: Advances in proteomics and genomics have identified various proteins and genetic materials in saliva that serve as potential biomarkers for periodontal disease. These include enzymes, immunoglobulins, and cytokines, which can help in understanding the disease's pathogenesis and therapeutic targets. [13,14]

Salivary Enzymes and Ions
Salivary enzymes and ions play significant roles in oral health. Lysozyme, an antimicrobial enzyme found in saliva, breaks down bacterial cell walls, helping to prevent plaque accumulation. Low lysozyme levels increase susceptibility to periodontal disease. Another enzyme, peroxidase, reduces harmful hydrogen peroxide levels and limits acid production in dental biofilm, thus decreasing plaque and gingivitis risk. Elevated peroxidase levels are observed in periodontal disease. Additionally, calcium ions in saliva have been studied as potential markers for periodontitis, with higher concentrations linked to patients with periodontal disease, although their diagnostic value remains uncertain.[15-17]

Non-Specific Biomarkers:
Several non-enzymatic, non-immunoglobulin proteins in saliva are linked to periodontal disease. Mucins (MG1 and MG2) protect and lubricate oral tissues, with MG2 playing a role in bacterial aggregation. Reduced MG2 levels can increase colonization by A. actinomycetemcomitans. Lactoferrin, an iron-binding glycoprotein, inhibits bacterial growth and is elevated during gingival inflammation. Histatin, another antimicrobial protein, neutralizes bacterial toxins and reduces inflammation. Fibronectin promotes bacterial adhesion and aids in tissue repair, while cystatins inhibit enzymes that cause tissue destruction. Platelet activating factor (PAF) is associated with periodontal inflammation, though its diagnostic potential remains unclear. Elevated proline levels in some patients suggest a link between amino acids and periodontal status, but no diagnostic significance has been established.[18-21]

Markers in Saliva via Gingival Crevicular Fluid (GCF)
As GCF travels through inflamed periodontal tissues, it picks up molecular markers that can be detected in whole saliva, offering insight into disease processes.[22]

Markers of Periodontal Soft Tissue Inflammation [23]
Proinflammatory cytokines, such as prostaglandin E2 (PGE2), interleukin (IL)-1beta, IL-6, and tumor necrosis factor-alpha, are released from periodontal tissues. These cytokines and enzymes like matrix metalloproteinases (MMP-8, MMP-9, MMP-13) degrade connective tissue and bone. PGE2 increases capillary permeability, causing inflammation, and stimulates fibroblasts and osteoclasts to produce MMPs, contributing to tissue destruction.

Markers of Alveolar Bone Loss. [24-26]
Biomarkers like alkaline phosphatase, osteocalcin, and collagen telopeptidases are associated with bone formation and resorption. MMPs, particularly MMP-8, MMP-9, and MMP-13, are involved in tissue degradation and remodeling, with elevated levels indicating disease progression. Pyridinoline cross-linked telopeptides of type I collagen serve as potential markers for bone resorption and periodontal disease progression. Specific Bone Loss Markers; 1. Telopeptide: Useful for detecting bone resorption and predicting future alveolar bone loss. 2. Osteocalcin: Elevated during periods of rapid bone turnover, it shows potential as a diagnostic marker when combined with other biomarkers. 3. Osteopontin: Elevated in

progressive periodontal disease, osteopontin levels decrease after treatment, indicating its promise as a salivary biomarker for disease progression.

Emerging salivary diagnostic tools

The utilisation of saliva for translational and clinical applications has become prominent. The salivary proteome and salivary transcriptome are increasingly pertinent tools for the early detection, progression, and therapeutic monitoring of periodontal diseases. Emerging technologies have demonstrated that salivary proteins and RNAs can detect oral cancer and Sjogren's syndrome. The stage is now prepared to employ these technologies for translational and clinical applications in periodontal diseases. [27]

Proteome of saliva: The proteome refers to the complete set of proteins encoded by the genome, while proteomics involves the analysis of the expressed segments of the genome. The proteomes in bodily fluids are significant owing to their substantial clinical potential as sources of disease biomarkers. A global analysis of human salivary proteomes can yield a thorough overview of oral and overall health. Moreover, the examination of salivary proteomes throughout the progression of complications may reveal morbidity indicators in the initial phase and track disease advancement. [26,27] Substantial advancements have been achieved in the cataloguing of human saliva proteins and the investigation of their post-translational modifications. Utilising both two-dimensional gel electrophoresis/mass spectrometry and "shotgun" proteomics methodologies, Hu et al. identified 309 unique proteins in human whole saliva. Denny et al. identified a total of 1166 salivary proteins: 914 from parotid fluid and 917 from the combined submandibular and sublingual fluids.[28] The salivary transcriptome is a developing concept. Alongside the salivary proteome, salivary transcriptomes (RNA molecules) were identified as being remarkably stable in saliva.[67] They incorporated mRNA molecules that cells utilise to transmit the directives encoded by DNA for subsequent protein synthesis. This discovery introduced a secondary diagnostic alphabet in saliva and provided a new pathway for salivary transcriptomic diagnostics.Invalid input. Please provide text for rewriting. [28]

Li et al. [29] discovered that RNA molecules increased in oral cancer tissues are similarly elevated in saliva, leading them to investigate the extent and intricacy of RNA present in human saliva. Various research teams, especially within forensic sciences, are concentrating on multiplex mRNA profiling to identify body fluids, such as saliva.[30,31]

Discussion:

Over the past 20 years, there has been a consistent uptick in research into periodontal disease monitoring instruments within the realm of periodontal diagnosis. Clinical and radiographic evaluations are the mainstays of periodontal disease diagnosis at the present time. These methods help find periodontal disease and confirm that the patient is healthy, but they don't tell you much about who could be at risk for periodontal breakdown in the future or which sites are most vulnerable. In order to diagnose periodontal disease, several salivary markers have been developed and tested. High levels of specificity and sensitivity are desirable in diagnostic tests. The multifaceted nature of periodontal disease makes it highly improbable that a single indicator will have both features. [3] For this reason, it is possible to get a more complete picture of the periodontal patient's health by using a panel of markers. The many benefits that saliva has over other biofluids have led to an uptick in its use as a diagnostic medium. Saliva is like a "mirror to the body" since it contains proteins and RNA that are similar to those in blood serum [32]. Because saliva is so readily available, it is much easier to collect samples, even when many are required. Because it is not invasive, patients are more likely to agree to the procedure, which helps make it less scary. There is no danger of cross-contamination or exposure to healthcare workers when collecting saliva instead of blood. Another factor that lowers the risk of transmitting infections like hepatitis and HIV is the lower concentration of antigens in saliva [35]. Saliva is less complicated to handle than blood or urine tests because it does not clot, and its increasing popularity may lead to a decline in testing costs over time. Unfortunately, the oneof-a-kind nature of salivary analysis means that it is still quite expensive.

The presence of inflammatory mediators and tissue-destructive molecules in gingival crevicular fluid (GCF) makes it a useful diagnostic tool for periodontitis. Nonetheless, GCF analysis is technically demanding, takes a long time, and requires a lot of manual labour because it requires sampling from individual tooth sites and measuring very small volumes of fluid (about 1 μL), which makes laboratory analysis more complicated and increases the risk of contamination from things like blood, saliva, or plaque [36]. On the other hand, there are a number of benefits to using salivary biomarker analysis. In comparison to GCF analysis, saliva collection is simple, painless, quick, and resource-efficient. On the other hand, GCF and whole saliva provide different diagnostic information [38-40].

The future seems bright for salivary diagnostic tests because of their ease of use and lack of invasive data collection. Complex oral fluids, such as GCF and saliva, may soon be manageable with the help of emerging technologies like lab-on-a-chip and microfluidic devices. These technologies have the potential to improve clinical decision-making and track the episodic progression of chronic infections like periodontitis by providing valuable insights into a patient's risk profile, disease activity, and treatment response [8].

Clinical Implications and Future Directions

Personalized Treatment: Salivary biomarkers can aid in developing personalized treatment plans by assessing individual disease risk and monitoring response to therapy, thus enhancing patientcentered care. [8, 11] Improved Diagnostic Accuracy: Combining multiple biomarkers can improve diagnostic accuracy and provide a more comprehensive assessment of periodontal health, potentially leading to better clinical outcomes. [3, 15] Potential for Routine Use: As research progresses, salivary biomarkers could become integral to routine periodontal care, offering a reliable and efficient method for disease management[1,8]

Conclusion

In conclusion, salivary biomarkers offer a promising and noninvasive approach for diagnosing and monitoring periodontal disease. As saliva mirrors the physiological state of the body, it contains valuable diagnostic information that can provide insights into disease progression, risk assessment, and treatment response. While traditional clinical and radiographic methods remain effective for assessing past disease, the use of saliva enhances the ability to identify patients at risk for future periodontal breakdown. Advances in technologies such as lab-on-a-chip and microfluidic devices further improve the potential for point-of-care diagnostics. Although there are still challenges, such as the cost of salivary testing and the need for more robust biomarker combinations, the future of salivary diagnostics in periodontics looks promising for more personalized and accurate patient care.

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