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Oral Biosensors: A Frontier in Non-Invasive Monitoring of Periodontal Health

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Abstract: Periodontitis is a complex inflammatory condition characterized by the gradual deterioration of the tissues that support the teeth, including the periodontal ligament and the alveolar bone. Timely diagnosis is crucial for preventing periodontitis. Diagnosing the condition involves various clinical and radiographic assessment methods that help classify the specific type of periodontitis affecting the patient. However, these methods have limitations; they do not provide real-time assessments of disease progression but instead indicate past tissue damage. Advancements in material science and nanotechnology have led to innovative approaches in periodontal diagnostics. One such development is the use of oral biosensors, which represent a significant leap in biomedical diagnostics and personalized medicine. Biosensors are compact, self-contained, analytical instruments designed to identify and quantify target substances. By enabling early detection and personalized treatment strategies, these biosensors hold great promise for improving patient outcomes and advancing oral healthcare.

Keywords: *Artificial Intelligence (Ai) In Dentistry, Biosensors, Oral Nanobiosensors, Personalized Periodontics, Point-of-Care Test, Salivary Diagnostics, Salivary Biomarkers.*

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I. INTRODUCTION

Periodontitis is a complex inflammatory condition characterised by the gradual deterioration of the tissues that support the teeth, including the periodontal ligament and the alveolar bone. It is characterised by the host's pathological response to a bacterial challenge initiated by a polymicrobial biofilm at the biofilm-gingival interface. Periodontitis affects approximately 10.5% to 12% of the global population [1].

Periodontitis is a rapidly progressing disease, so timely diagnosis is crucial to prevent further progress. A range of clinical and radiographic assessment methods are used to accurately classify the specific periodontitis affecting a patient. Recent research aims to enhance diagnostic precision and identify the precise risk factors associated with periodontitis, ultimately pinpointing the exact cause of the disease.

Various oral fluids, like GCF and saliva, have been extensively researched for specific biomarkers related to inflammation of the attachment apparatus. Saliva is a rich source of valuable biomarkers that offer crucial insights into an individual's health status. These biomarkers encompass a variety of categories, including proteins, nucleic acids, hormones and metabolites, each providing distinct information about different physiological and pathological conditions.

These innovative biomarkers and sensing methods have laid the foundation for the development of sophisticated intraoral biosensors. In recent years, the focus has been on biosensors that facilitate health surveillance, prevention, and treatment in real-time. Biosensors are an exciting addition to the world of nanomedicine and technology [2] .

II. ENHANCING PERIODONTAL DIAGNOSIS: ADDRESSING CHALLENGES AND UNMET NEEDS

One of the primary challenges of periodontal diagnosis lies in the subjectivity of clinical assessments. Diagnosis often relies on clinical observations such as probing depth, bleeding on probing (BOP), and clinical attachment loss (CAL), which can vary significantly between clinicians due to differences in technique and interpretation. While probing offers insights into the disease, it is susceptible to errors caused by inflammation and operator variability. Similarly, radiographs reveal bone loss but fail to detect soft tissue conditions or real-time disease activity.

Another major challenge is identifying active disease. Current diagnostic methods focus on assessing past damage, such as bone or attachment loss, rather than detecting ongoing disease activity, which delays timely intervention. Technological advancements in biomedicine, including highly sensitive diagnostic platforms and machine learning algorithms, have revolutionised periodontal research. These developments have revealed the limitations of the standard clinical approach in providing reliable and patient-specific diagnostic information.

Real-time diagnostic tools capable of measuring biomarkers in saliva, gingival crevicular fluid, or blood are crucial for identifying active disease and predicting its progression. Integrating artificial intelligence (AI) into diagnostics could help analyse clinical and radiographic data more consistently, developing predictive models to assess disease risk and tailor treatment plans. Personalised diagnostic approaches tailor precise management strategies that incorporate genetic, microbiological, and lifestyle factors, leading to better individual care.

III. BIOSENSORS

The development and implementation of modern technologies that utilise specific biomarkers at the chair-side are expected to enhance clinical diagnostic and prognostic insights. The rapid progress and seamless integration of materials science, soft electronics, sensing techniques, and information technologies have propelled medical science into new frontiers. Biosensors, compact, self-contained analytical instruments, are utilised for the identification and quantification of target substances. Clark and Lyons pioneered the field with the creation of the first biosensor, an enzyme-based glucose sensor [3].

According to the International Union of Pure and Applied Chemistry (IUPAC), “a biosensor is a device that uses specific isolated enzymes- mediated biochemical reactions to detect chemical compounds either by thermal, electrical or optical signals” [4].

Salivary biosensors stand at the forefront of diagnostic technology, harnessing the power of saliva to monitor and detect a wide range of biological markers. These innovative sensors provide a non-invasive, efficient, and easily accessible approach to real-time health monitoring. Looking ahead, wearable intraoral bio-electronic platforms and portable POC devices are anticipated to play an increasingly significant role in clinical investigations and diagnoses, offering substantial benefits compared to traditional laboratory equipment and procedures. The aim is to anticipate and prevent future occurrences of periodontal infections by meticulously examining current trends and diagnostic methods.

Lab-on-a-chip (LOC) devices have transformed biochemical analysis by significantly reducing the consumption of reagents and samples, thereby enhancing resource efficiency [5]. Their compact design significantly reduces analysis times, ensuring timely results in medical settings. The cost-effectiveness of these assays, with fewer technological constraints, makes them ideal for point-of-care testing in diverse environments. LOC devices have the potential to transform diagnostic procedures, drastically reducing waiting times for accurate diagnoses and expediting treatment. Concurrently, advancements in biotechnology have led to the development of sophisticated biosensors and microelectromechanical systems (MEMS), which integrate precision and miniaturization to achieve improved detection across diverse applications [6].

➢ *Components*

A biosensor comprises three essential components:

- Bioreceptor: Detects the target biomolecule and generates a stimulus. Examples include enzymes, antibodies, DNA strands, or whole cells.
- Transducer: Converts the biological interaction into an electrical or optical signal.
- Signal Processor: Amplifies, processes, and displays the signal in a readable format.

➢ *Key Selection Criteria for Intraoral Biosensors:*

For periodontitis detection, intraoral biosensors must exhibit:

- *High Sensitivity & Specificity:*

Must accurately detect key periodontal biomarkers such as:

- ✓ Inflammatory cytokines (IL-1β, TNF-α)
- ✓ Matrix metalloproteinases (MMP-8)
- ✓ pH variations in oral fluids

- *Low Limit of Detection (LOD):*

Enables early-stage disease diagnosis by detecting biomarkers at trace concentrations.

- *Real-Time & Multiplex Detection:*

Simultaneous detection of multiple biomarkers enhances diagnostic reliability.

➢ *Working Principle of Biosensors*

A salivary biosensor is a non-invasive analytical device that detects specific biological or chemical markers in saliva by integrating a bioreceptor, transducer, and signal processor. The bioreceptor selectively binds to a target analyte, such as glucose, hormones, pathogens, or drugs, present in the saliva. Through a process called the electro-enzymatic approach, enzymes are transformed into corresponding electrical signals, typically in the form of current, with the assistance of a transducer. When a biosensor detects a change, its transducer turns this into an electrical, optical, or mechanical signal. This signal is then processed and displayed in a simple, readable format, so health issues like infections, stress, or metabolic problems can be tracked in real time.[7]

IV. CURRENT LANDSCAPE OF ORAL BIOSENSOR TECHNOLOGIES

➢ *NanoBiosensors*

Biosensor related discovery has several advantages over traditional approaches, including affordability, simplicity of running, miniaturisation, and the lack of the need for an expert to assay the data. As a result, integrating developments in biosensing with nanotechnology aids in providing a considerable enhancement in strategies for discovering and understanding different conditions. In this context, gold nanoparticles (AuNPs), quantum dots (QDs), dendrimers, metal oxides, carbon-nanocomposites, and other nanomaterials(NMs) have been employed to fabricate nano biosensors. Nanobiosensors can detect crucial pathogenic bacteria similar as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans directly within clinical samples, with some detecting limits as low as 1 ng/ mL for gingipains, a crucial factor in periodontitis [8].

Kim C- Y.et al, developed a multicolorimetric Alkaline phosphatase (ALP) and IL- 1β detecting platform using an Ag nanoplate transducer [9]. Garam Ba and co-workers proposed a detecting material that can directly and widely detect ppb-levels of methyl mercaptan(CH_3SH) in exhaled breath, pivotal for early opinion of periodontitis [10]. Zhang T, et al used actuated AgNPs as a substrate for Surface-Enhanced Raman Spectroscopy (SERS) to enhance P. gingivalis signals in diagnosing periodontitis [11]. Yao M, et al. are also exploring the use of Nano- Graphene Oxide Quantum Dots (GOQDs) as fluorescent labels for periodontal ligament stem cells (hPDLSCs). The study stated that GOQDs could access the cell membrane and increase luminescence intensity, demonstrating their association with living cells. Overall, these advancements in flouro-luminescence discovery and imaging have the eventuality to revise dental care [12].

- *Point- of- Care Diagnostic Platforms*

The development of point- of- care (POC) devices has revolutionized periodontal diagnostics by furnishing rapid-fire, chairside assessment capabilities. These systems generally operate within 3-10 minutes with minimum sample volumes (10- 20 μL) and demonstrate perceptivity in the nanomolar to picomolar range [13-14]. POC platforms integrate microfluidics, optics, and data accession software to produce portable, self-contained diagnostic [14].

Periodontitis diagnosis is rapidly progressing towards approaches that can identify and assess periodontal threat using objective criteria like biomarkers Matrix metalloproteinases- 8 (MMP- 8), IL- 1β, and tumour necrosis factor alpha (TNF- α) are the biomarkers that have garnered the utmost attention. This is because these biomarkers are directly linked to the destruction of periodontal structure [15].

V. KEY BIOMARKERS AND DETECTION METHODS

- *Detection Methods*

- *Matrix Metalloproteinase - 8 (MMP- 8)*

MMP- 8, a significant biomarker for periodontal diagnosis, has been shown to separate between periodontal health, gingivitis, and periodontitis with high detection rate (74.2- 82.) [16-17]. A prototype antibody-associated biosensor using microelectromechanical piezoelectric surface acoustic wave (SAW) technology achieved an AUC value of 0.89, similar to traditional ELISA (AUC 0.93) [17]. A new nanobiosensor demonstrated favorable performance, with discovery limits suitable for clinical operations. It showed significant correlations with established immunofluorescence assays and could cover treatment response in periodontitis cases [18]. The Periosafe ® test combines lateral flow technology with ELISA to detect active MMP-8 (aMMP- 8) in mouth wash samples, furnishing readouts that relate with quantitative reductions in MMP- 8 levels post-treatment [19]. Surface Plasmon Resonance- POF technology may produce largely sensitive biosensors to cover salivary MMP- 8 levels. A functionalised SPR- POF biosensor detected total MMP- 8 with high selectivity and low LOD in both buffer and saliva samples [20]. A new voltammetric biosensor detects salivary MMP- 8, a pivotal index of periodontitis progression. Designed for use at the pulp and canal (POC) without laboratory machinery, it uses a GPH screen-electrode modified with AuNSs and antibodies specific to MMP- 8. Disposable and cost effective, it requires minimum test media and medication time [21].

- *Interleukin- 1β (IL- 1β)*

IL- 1β, a pivotal pro-inflammatory cytokine, plays a vital part in the progression of periodontitis. Advanced biosensors have been developed to descry IL- 1β, including electrochemiluminescence immunosensors that can descry levels as low as 0.64 fg/ mL in gingival crevicular fluid. These detectors demonstrate exceptional selectivity and anti-interference capabilities, making them suitable for detecting IL- 1β in complex natural matrices [22]. Research has shown a strong correlation between IL- 1β levels and clinical parameters like probing depth and clinical attachment loss, making it a precious biomarker for both individual and prognostic operations [23]. Salivary IL- 1β discovery has particularly better for non-invasive periodontal assessment [24]. The proposed IL- 1β SPR- POF point- of- care test meets WHO criteria for point- of- care technologies and is a promising tool for early periodontitis detection and monitoring complaint progression and remedial interventions. Salivary IL- 1β measures from healthy and periodontitis cases were similar to those from ELISA, the gold standard for cytokine determination, validating the biosensor for precise IL- 1β discovery. Also, the device can measure other labels linked to periodontitis pathology, similar as IL- 6, MMP- 8, MIP- 1α, and malondialdehyde [25]. A surface-MIP- based biosensing system, with a strategically designed electropolymerised functional thin film, creates natural recognition spots, frequently appertained to as antibody mimics. To enable immediate opinion, the MIP-enabled electrodes are integrated with a smartphone- linked mobile POCT device. A custom relay circuit system provides a user-friendly interface for real-time IL- 1β position quantification [26].

- *Tumor Necrosis Factor-α (TNF-α)*

TNF- α biosensors have demonstrated significant mileage in periodontitis detection, with studies showing positive correlations between TNF- α and periodontal parameters including plaque index, gingival index, probing depth, and clinical attachment loss. Advanced biosensing platforms have been developed that can descry TNF- α in both saliva and gingival crevicular fluid, furnishing comprehensive assessment of inflammatory status [27-28].

➢ *Advanced Biosensor Platforms*

- *Electrochemical Sensing Systems*

Electrochemical biosensors have surfaced as the most promising platform for oral disease discovery due to their high perceptivity, fast response times, and are implicit for miniaturization [29]. These systems use varied discovery mechanisms including amperometry, voltammetry, potentiometry, and electrochemiluminescence [30]. Recent developments include flexible screen-printed electrochemical platforms and molecularly ingrained polymer detectors with deep learning integration[31-32].

- *Microfluidic Lab-on-Chip Systems*

Integrated microfluidic platforms enable sophisticated sample processing and analysis within miniaturized biosensors. These systems combine sample pretreatment (filtering, enrichment, mixing) with electrophoretic immunoassays to measure analyte concentration in minimally pretreated saliva samples. The technology has been successfully enforced for detecting multiple periodontal biomarkers, perfecting individual diagnostic accuracy [14].

- *Wearable Biosensor Technologies*

The development of wearable oral biosensors represents a significant advancement toward continuous health monitoring. Innovative platforms include instrumented mouthguards capable of real-time monitoring with wireless data transmission. These devices integrate miniaturized electronics, Bluetooth connectivity, and smartphone applications for comprehensive health assessment. A notable example is the wireless mouthguard biosensor system that demonstrated successful monitoring of salivary biomarkers with high sensitivity, selectivity, and stability over extended periods. Similarly, battery-free dental patches using near-field communication technology enable wireless monitoring and controlled drug delivery. Implantable and flexible electronic biosensors utilise hydrogel-based or biocompatible materials for long-term intraoral monitoring [33-34].

VI. DRAWBACKS OF ORAL BIOSENSORS

Oral biosensors represent a groundbreaking advancement in the field of periodontics, offering the potential for non-invasive and real-time monitoring of biomarkers associated with periodontal disease. These innovative devices could revolutionize how dentists and patients manage oral health; however, their integration into clinical practice is hampered by several significant challenges.

A primary concern is biocompatibility. Many materials utilized in the fabrication of these sensors may provoke irritation or even adverse reactions within the sensitive environment of the oral cavity. This issue becomes even more pronounced considering the oral environment's inherent variability, characterized by fluctuations in pH, temperature, and enzymatic activity. Such dynamic conditions can adversely affect the sensors' stability and accuracy, posing a considerable challenge to their functionality.

Furthermore, the phenomenon of biofouling can severely diminish sensor performance. This occurs when plaque, proteins, and other organic substances accumulate on the sensor surfaces, obstructing their ability to function effectively. Coupled with this is the challenge of sensitivity and specificity; the typically low concentrations of target biomarkers in saliva, combined with the possibility of cross-reactivity, can result in misleading readings that may compromise patient assessment and treatment.

The lifespan of oral biosensors is another critical limitation. These devices often succumb to degradation in the mouth's moist and enzyme-rich environment, necessitating frequent recalibration to maintain consistent and reliable results. Additionally, the high costs associated with developing and manufacturing complex biosensors present obstacles to widespread adoption, limiting access for many practitioners and patients.

Equally important is the need for seamless integration with data analysis systems, which is vital for maximising the utility of these biosensors. However, challenges related to software availability and user-friendliness can impede effective implementation in clinical settings. Lastly, patient compliance is a significant factor in the success of these devices; discomfort may deter individuals from using them regularly, and improper handling or inadequate hygiene practices can further compromise sensor performance.

These multifaceted limitations underscore the pressing need for ongoing research and innovation aimed at enhancing the practicality and reliability of oral biosensors in the realm of periodontics. As efforts continue to address these challenges, the promise of oral biosensors in transforming periodontal disease management remains both hopeful and achievable.

VII. FUTURE PROSPECTS OF BIOSENSORS IN PERIODONTAL DIAGNOSTICS

The future of biosensor technology in periodontics holds great promise, with groundbreaking advancements that will revolutionise disease detection, monitoring, and management. These next-generation biosensors, powered by AI, miniaturisation, and wireless connectivity, will offer real-time, non-invasive, and highly accurate diagnostics. AI algorithms can analyse biomarker trends and predict disease progression before symptoms worsen [35]. Nanotechnology and flexible electronics will lead to compact, lightweight, and user-friendly biosensors. Soft, stretchable, and implantable sensors will seamlessly integrate with oral tissues for enhanced comfort and compliance. Wireless biosensing enables remote patient monitoring and real-time data sharing via cloud-based systems. Biosensors embedded in scaffolds or dressings track healing progress and provide treatment efficacy feedback [36].

VIII. CONCLUSION

Periodontitis is a serious global health issue that requires accurate diagnostics and timely intervention to prevent tooth loss. Researchers are focused on developing advanced diagnostic tools to detect the onset and progression of this disease. While blood has traditionally been the standard diagnostic fluid, oral fluids like saliva and gingival crevicular fluid offer advantages such as non-invasive collection, smaller sample volumes, and greater sensitivity. Biosensors, which aid in point-of-care diagnostics and monitoring, have the potential to revolutionise personalised healthcare by reducing the need for invasive methods. However, much of the research on dental nanomaterials has been confined to in vitro studies, leaving limited evidence of their effects in vivo. Further research is crucial to make biosensors more cost-effective and readily available for widespread clinical use.

Oral biosensors represent a promising advancement in interdisciplinary dentistry due to their ability to non-invasively monitor a wide array of oral and systemic health parameters in real time. Oral biosensors can detect biomarkers for oral diseases such as periodontitis, dental caries, and oral cancers, enabling earlier and more precise diagnoses compared to traditional methods.

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