Review Article

Precision Medicine in Periodontics: A Literature Review

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Abstract:
Periodontitis remains a globally prevalent chronic inflammatory disease with profound public health implications. Its rising incidence and adverse social consequences necessitate innovative preventive and therapeutic strategies. Beyond its local impact, periodontitis is increasingly recognized for its role in exacerbating systemic health disorders, underscoring the urgency for more refined management approaches. Conventional diagnostic tools such as probing depth, clinical attachment level, tooth mobility, and radiographic evaluation of alveolar bone offer limited predictive value and therapeutic guidance due to the complex and multifactorial nature of periodontal diseases. Precision periodontics, integrating advances in genomics, bioinformatics, and patient-specific biomarkers, aims to shift care toward personalized treatment paradigms. Despite its promise, the clinical application of this model in periodontology is still in its nascent stages, mainly due to the paucity of clinically validated biomarkers. This article critically examines the evolving role of personalized diagnostics in periodontics and evaluates the current and prospects of biomarker-driven precision care in managing periodontal disease.

Keywords: Precision periodontics, patient-specific biomarkers, biomarkers, biomarker-based diagnostics, periodontitis.

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INTRODUCTION:

Periodontitis is a major global health burden, ranked as the 11th most prevalent disease worldwide according to the Global Burden of Disease Study (2016) [1]. Severe forms affect approximately 20% to 50% of the population, significantly contributing to tooth loss, which impairs oral function, facial aesthetics, self-esteem, and overall quality of life [2]. These consequences have driven a global emphasis on enhancing preventive and therapeutic measures to improve diagnostic accuracy, clinical outcomes, and reduce the financial strain of periodontal treatment.

At the core of periodontal disease lies the complex interaction between dysbiotic microbial communities in dental plaque and the host's dysregulated immune-inflammatory response [3]. Effective treatment thus necessitates disruption of the pathogenic biofilm. Given the multifactorial nature of periodontitis, biomarker-based diagnostics offer

promising advantages over traditional clinical and radiographic assessments. Biomarkers allow for individualized risk assessment, early detection, prognosis, and tailored therapeutic interventions that better align with each patient's unique biological profile [4].

In vitro diagnostics (IVDs), already influential in guiding more than 60% of medical decisions, are increasingly being explored in dentistry as tools for enhancing diagnostic precision and therapeutic efficacy. The 2017 classification of periodontal and peri-implant diseases marked a pivotal moment with the inclusion of biomarkers, setting the foundation for integrating precision medicine into periodontology [5]. Precision medicine, an approach that personalizes care based on a combination of genetic, molecular, phenotypic, and psychosocial characteristics, is now transforming multiple medical disciplines. However, its integration into periodontal practice remains limited, primarily due to the absence of thoroughly validated diagnostic biomarkers.

LIMITATIONS AND COMPLEXITIES OF CONVENTIONAL APPROACHES

Traditional diagnostic modalities in periodontology chiefly clinical probing and radiographic evaluation primarily assess parameters such as clinical attachment loss, probing depth, and alveolar bone resorption. While these measures provide historical insights into periodontal tissue destruction, they fall short in detecting ongoing disease activity or predicting future progression [6]. Additionally, individual variability in genetic susceptibility and temporal disease expression poses further diagnostic challenges, making it difficult to apply a one-size-fits-all diagnostic approach.

Recent developments in biomedical sciences, particularly in high-throughput omics technologies, advanced diagnostic platforms, and artificial intelligence, have exposed the deficiencies of conventional diagnostic strategies in managing periodontal diseases [7]. The keystone pathogen hypothesis has significantly reshaped our understanding of the microbial etiology of periodontitis, particularly with the identification of Porphyromonasgingivalis as a key pathogen capable of orchestrating dysbiosis within the subgingival microbiome [8,9]. Rather than being a simple result of pathogenic colonization, periodontitis is now viewed as the outcome of a complex interplay between a dysbiotic microbial community and the host's aberrant inflammatory response [10,11].

This paradigm shift highlights the importance of evaluating not only the microbial composition but also host immune responses and other contributing risk factors. Environmental influences, systemic health conditions, genetic polymorphisms, and even viral or fungal coinfections can all compromise host defences. Individuals with hyper-responsive or genetically predisposed immune systems are particularly vulnerable to aggressive and refractory forms of periodontal disease [12]. Consequently, conventional clinical and radiographic tools, which offer limited insight into such multifactorial mechanisms, are increasingly seen as inadequate for comprehensive diagnosis and personalized treatment planning. The integration of biomarkers into diagnostic workflows offers the potential for more precise, real-time assessment of disease presence, progression, and therapeutic response [13].

SUPERIORITY OF PRECISION DIAGNOSIS AND THERAPY OVER TRADITIONAL METHODS

The precision medicine paradigm offers a transformative approach to periodontal care by integrating molecular, genetic, environmental, and behavioural data to tailor prevention and treatment strategies to the individual. Unlike traditional methods, this approach allows for the development of highly targeted therapeutic regimens that align with a patient's specific genetic and biological profile, reducing the risk of adverse effects and enhancing drug efficacy.

Furthermore, precision diagnostics can stratify patients based on predicted therapeutic responsiveness, thereby improving clinical trial efficiency by identifying responders and non-responders at an early stage. This reduces the time,

cost, and attrition associated with drug development. Precision approaches also enhance public health strategies by enabling early identification of at-risk individuals, thus facilitating preventive interventions, and reducing the burden of disease over time. Overall, precision periodontics represents a paradigm shift from reactive, uniform interventions to proactive, individualized healthcare delivery.

BIOMARKERS IN PRECISION PERIODONTICS

Biomarkers are quantifiable indicators that reflect physiological, pathological, or therapeutic responses within the body. They provide dynamic insight into ongoing biological activities by detecting specific molecular signatures such as proteins, nucleic acids, or metabolic by- products produced by cells or tissues in response to genetic, epigenetic, or environmental factors [14]. In the context of periodontal diagnostics, biological samples commonly used for biomarker analysis include dental plaque, saliva, and gingival crevicular fluid (GCF). The classification of biomarkers is typically informed by patient medical history, clinical examination, and diagnostic testing to determine the disease stage and activity level [15].

Predictive Biomarkers

Predictive biomarkers are instrumental in identifying individuals with an elevated risk of developing periodontal disease, enabling clinicians to tailor preventive strategies, refine screening protocols, and modify risk-related behaviours before clinical manifestation. One of the most prominent classes of predictive markers is single nucleotide polymorphisms (SNPs), which can highlight inherited susceptibility to periodontal disease [15].

Certain immunogenetic profiles have been associated with inadequate clearance of periodontal pathogens, contributing to exaggerated tissue destruction. For instance, SNPs in genes such as Interleukin-1 β (IL1β), Interleukin 1 Receptor Antagonist (IL1RA), Fc gamma receptor IIb (FcγRIIb), Vitamin D Receptor (VDR), and Toll-Like Receptor 4 (TLR4) have been implicated in heightened vulnerability to aggressive periodontitis. Conversely, polymorphisms in IL1 β, IL1RN, IL6, IL10, VDR, CD14, TLR4, and matrix metalloproteinases 1 (MMP1) are thought to contribute to the general risk of chronic periodontitis [16].

In a study conducted by Schulz et al., the relationship between IL-1 gene cluster polymorphisms and the subgingival colonization of Aggregatibacteractinomycetemcomitans was examined. While a correlation between the genetic profile and microbial colonization was observed, the findings did not conclusively establish this as an independent risk factor for periodontitis progression [17].

Prognostic Biomarkers

Prognostic biomarkers are utilized after disease onset and are typically static, providing crucial information on disease behaviour, anticipated progression, and response to therapy. Unlike predictive markers, they do not require temporal change to be clinically useful. These markers aid clinicians in selecting optimal treatment modalities, anticipating complications, and crafting individualized maintenance plans to support long-term periodontal health [18].

They are essential for determining both the stage (severity and extent) and grade (rate of progression and risk factors) of the disease parameters vital to forming an accurate prognosis and evidence-based treatment roadmap [19]. A comprehensive meta-analysis by Feng et al. demonstrated a significant association between the IL-1A (-889C/T) polymorphism and increased susceptibility to chronic periodontitis across diverse ethnic groups, including African, European, and American populations [20].

Diagnostic Biomarkers in Periodontics

Diagnostic biomarkers encompass a broad spectrum of biochemical and microbiological indicators that reflect active disease processes in periodontal tissues. These markers are particularly valuable in assessing disease activity, gauging the patient's response to therapy, and monitoring compliance with periodontal treatment regimens. Included within this

group are surrogate biomarkers representing inflammatory status, soft and hard tissue metabolism, and host response mechanisms [21].

INFLAMMATORY BIOMARKERS

Inflammatory markers serve as crucial indicators of the host's immunoinflammatory response and are extensively investigated in the context of both gingivitis and periodontitis. These include proinflammatory and anti-inflammatory cytokines, which can help assess disease severity, progression, and therapeutic responsiveness.

Key cytokines from the T-helper cell (Th) subsets include:

- Th1: IL-1β, IFN-γ, TNF-α
- Th2: IL-4, IL-6, IL-10
- Th17: IL-17
- Additional: IL-8

Among these, Th1 and Th17 cytokines tend to be elevated in active periodontal disease and generally diminish following effective therapy, making them more specific markers of disease activity. In contrast, Th2 cytokines, while still important, may have comparatively lower diagnostic specificity [22–25].

An imbalance between reactive oxygen species (ROS) and antioxidant defences is another hallmark of periodontal pathology. Oxidative stress markers such as malondialdehyde, nitric oxide, total oxidant status (TOS), total antioxidant capacity (TAC), and 8-hydroxydeoxyguanosine (8-OHdG) are measurable in saliva and show sensitivity to periodontal treatment, offering insights into systemic and local oxidative burden. Salivary profiles tend to be more diagnostically reliable than those from GCF in this context.

Calprotectin, a calcium- and zinc-binding protein with immunomodulatory functions, inhibits immunoglobulin production and plays a defensive role against bacterial invasion, especially Porphyromonasgingivalis, by upregulating at inflammatory sites. Elevated levels in GCF are indicative of active periodontal inflammation [26,27]. In a comparative study, Becerik et al. evaluated calprotectin, osteocalcin, and cross-linked N-terminal telopeptide (NTx) levels in GCF across various periodontal conditions. They concluded that while elevated calprotectin reflected ongoing inflammation, fluctuations in osteocalcin and NTx levels suggested altered bone metabolism in periodontitis [28].

Soft Tissue Biomarkers

Soft tissue degradation markers, particularly MMPs, are pivotal in the breakdown of extracellular matrix components. Elevated levels of MMP-8 and MMP-9 are consistently found in periodontitis, while MMP-13 and MMP-8 are also notably elevated in peri-implantitis, indicating their potential use in peri-implant diagnostics.

Additionally, factors involved in tissue repair and angiogenesis, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), are found at increased levels in diseased gingival tissues. VEGF is upregulated in epithelial and endothelial cells of periodontitis-affected sites, suggesting its role as a potential biomarker for healing potential and disease activity [29].

A comprehensive meta-analysis by Ghassib et al. evaluated the utility of biomarkers in peri- implant crevicular fluid (PICF) to differentiate healthy implants from those affected by peri- implant mucositis or peri-implantitis. The findings supported the diagnostic value of IL-1β and IL-6, which can serve as reliable adjuncts to clinical evaluation when identifying peri-implant disease [30].

Bone Turnover Markers (BTMs)

Bone turnover markers provide insights into the dynamic processes of bone resorption and formation in periodontal tissues. Central to this regulation are the molecules receptor activator of nuclear factor-kappa B (RANK) and its ligand RANKL, which promote osteoclast differentiation and bone resorption. In contrast, osteoprotegerin (OPG) acts as a decoy receptor for RANKL, inhibiting bone resorption and supporting bone remodelling [31]. While these markers are closely linked with the pathophysiology of bone loss in periodontitis, their precise diagnostic utility in assessing real-time

disease activity remains to be conclusively established.

Osteonectin, a glycoprotein involved in mineralization and matrix organization, has shown promise as a sensitive marker for early detection of periodontal disease, outperforming the N- terminal propeptide of type I collagen (PINP) in sensitivity.

Additionally, osteopontin (OPN), a multifunctional phosphoprotein essential in bone remodelling, has been inversely correlated with probing pocket depth, suggesting a potential regulatory role in disease modulation and wound healing [32].

Histopathological Markers

Although not routinely employed in clinical periodontology, histopathological biomarkers can offer critical insights into the cellular and molecular mechanisms underpinning disease initiation, progression, and severity. These markers may also aid in identifying new, clinically applicable biomarkers by elucidating tissue-level changes in inflammatory and degenerative periodontal conditions.

GINGIVAL CREVICULAR FLUID AS A BIOMARKER SOURCE

GCF has long been recognized for its rich content of diagnostic biomarkers, reflecting both local host response and microbial activity in periodontal pockets. Due to its proximity to the site of periodontal pathology, GCF is a particularly informative source for assessing site- specific disease activity.

GCF contains a diverse array of biomarkers, including interleukins, tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2), osteocalcin, RANK, OPG, RANKL, transforming growth factor-beta1 (TGF-β1), MMPs, acid and alkaline phosphatase (ALP), aspartate aminotransferase (AST), IL-1RA, IFN-γ among others.

These molecular markers are typically classified into six functional categories: indicators of cell death, markers of tissue degradation, inflammatory mediators, regulators of bone resorption, components involved in bone formation and mineralization, and other miscellaneous biomarkers. Studies have demonstrated strong associations between GCF levels of proteases and collagenases and clinical parameters such as pocket depth. Barros et al. emphasized the utility of GCF as a reservoir of biomarkers that distinguish active disease sites from quiescent ones.

Similarly, in an extensive review, Kaur et al. (2017) catalogued a wide array of host defence mediators in GCF, reinforcing its value in biomarker discovery for periodontitis. However, despite its diagnostic promise, GCF sampling is technique-sensitive and may pose challenges in routine chairside applications [33].

Saliva as a Biomarker Source

Saliva presents a highly practical, non-invasive medium for periodontal diagnostics. Its ease of collection, minimal processing requirements, and continuous production make it an attractive alternative to more complex biofluids. Saliva contains a diverse array of molecules, including cytokines, enzymes, DNA/RNA fragments, antibodies, hormones, and growth factors, all of which may contribute to a comprehensive assessment of periodontal and peri-implant health.

Commonly analysed salivary biomarkers in periodontitis include IL-1β, IL-6, IL-8, IL-10, IL- 12, TNF-α, MMP-3, MMP-8, MMP-9, and TIMP-1, all of which have shown elevated levels in disease states. Additionally, markers of osteoclastogenesis, such as RANK, RANKL, and OPG, and oxidative stress-related proteins like malondialdehyde, urate, ascorbate, and myeloperoxidase, are found in higher concentrations in individuals with peri-implantitis.

Despite the diagnostic potential of salivary analysis, a consensus on standardized biomarker panels for clinical application is lacking. The heterogeneity in study designs and outcome measures hinders the development of universally accepted biomarkers for personalized periodontal care. Nonetheless, MMPs and interleukins remain among the most promising

salivary indicators, holding considerable potential for future diagnostic platforms in periodontology [34].

Strategies for Implementing Precision in Periodontics
The integration of cutting-edge technologies into periodontics is paving the way for a shift toward precision-based diagnosis and treatment. Although still in the nascent stages, precision periodontics leverages multi-omics platforms, digital tools, and advanced analytics to tailor care to individual patient profiles.

The selection of biomarkers is highly dependent on the diagnostic objective. For instance:

- Microbiological profiling benefits from metagenomics, meta-transcriptomics, and culturomics to characterize the subgingival microbial environment.
- Proteomic analyses are crucial for quantifying cytokines and other protein mediators involved in the inflammatory response.
- Transcriptomics and metabolomics may be employed for a deeper understanding of host-pathogen interactions and metabolic changes.

Despite their promise, biomarker analyses face challenges including false positives, false negatives, and variability in results. These issues necessitate the use of high-fidelity equipment and skilled personnel to ensure reproducibility and clinical relevance.

Precision Dentistry and the Role of Advanced Technology

Precision dentistry has significantly enhanced diagnostic accuracy and therapeutic outcomes through the adoption of digital and automated systems. Modern clinics are increasingly incorporating real-time vital sign monitoring, digital charting, and equipment diagnostics into routine care.

- Radio-Frequency Identification (RFID) is used to track instruments and streamline clinical workflows.
- Computer-Aided Design/Computer-Aided Manufacturing (CAD/CAM) has revolutionized prosthodontics by replacing traditional impression techniques with precise digital workflows.
- 3D scanning technologies have eliminated the discomfort associated with conventional dental impressions, improving the patient experience.
- Operating microscopes now support enhanced visualization during delicate procedures such as endodontic therapy and periodontal microsurgery, leading to better clinical precision and outcomes [35].

ARTIFICIAL INTELLIGENCE (AI) IN PRECISION PERIODONTICS

Artificial intelligence is increasingly synergizing with precision dentistry to enhance patient care. AI algorithms are adept at processing and interpreting large, complex datasets, aligning well with the personalized nature of precision medicine.

Key contributions of AI in this domain include:

- Improved diagnostic accuracy through pattern recognition and predictive modelling.
- Personalized treatment planning based on integrated data analysis.
- Predictive maintenance of dental equipment to reduce downtime.
- Patient engagement tools such as AI-powered virtual assistants to enhance adherence and education.
- Accelerated research and development, fostering the discovery of novel therapeutic agents and interventions.

Despite these advantages, AI integration must address challenges such as data privacy, regulatory compliance, education and training of clinicians, and cost-effectiveness to be fully realized in clinical settings [36].

Barriers to the Implementation of Precision Periodontics

Fig 1- Barriers to the Implementation of Precision Periodontics

A range of systemic, technological, and educational barriers must be addressed to facilitate the successful implementation of precision periodontics (illustrated in Figure 1).[37]

- **Data Integration-** The heterogeneity of data from genomic, clinical, and behavioural sources complicates integration. This challenge can be mitigated by adopting electronic health records (EHRs), common data models, and interoperable precision medicine platforms.
- **Multifactorial Etiology-** Periodontitis involves complex host-microbe interactions and systemic influences, complicating biomarker discovery. Collaborative research and the application of machine learning algorithms may help untangle these complexities.
- **Limited Microbiome Understanding-** The structure and function of the periodontal microbiome remain incompletely characterized, limiting the efficacy of targeted antimicrobial therapies. Techniques such as 16S rRNA gene sequencing and next- generation antimicrobials offer potential breakthroughs.
- **Awareness and Education Gaps-** Many dental practitioners are unfamiliar with advanced diagnostics and personalized care approaches. Implementation can be enhanced through continuing education programs, hands-on workshops, and online learning platforms.
- **Regulatory Challenges-** Rapid innovation often outpaces existing regulatory frameworks. Engagement with regulatory bodies is essential to establish clear guidelines, validation protocols, and standardized metrics.
- **Patient-Cantered Barriers-** Socioeconomic disparities, cultural attitudes, and behavioural compliance significantly impact treatment success. Emphasis on individualized care plans, cultural competence, and patient empowerment strategies is crucial [38].
- Precision periodontics represents a paradigm shift in the diagnosis and management of periodontal diseases by moving away from generalized approaches toward individualized care. This evolution is being driven by advances in biomarker research, digital dentistry, and artificial intelligence. However, the successful clinical integration of precision strategies hinges on the rigorous validation of biomarkers and the development of reliable, standardized diagnostic platforms.
- Future research must prioritize the design and implementation of practical biomarker evaluation protocols, with a strong emphasis on point-of-care testing (POCT). Despite the wealth of molecular insights gained through recent scientific efforts, the lack of validated periodontal biomarkers for routine diagnostic use remains a critical bottleneck. As the field advances, it becomes imperative to identify and clinically validate the most specific and patient-relevant biomarkers, enabling the transition from research to personalized clinical application.
- Realizing the full potential of precision periodontics will require interdisciplinary collaboration, regulatory alignment, continuous professional education, and patient engagement. With these efforts, precision periodontics can progress from an emerging concept to a transformative clinical reality in periodontal healthcare.

CONCLUSION-

The emergence of precision periodontics holds significant potential to transform periodontal diagnosis and treatment by enabling highly individualized care. Achieving this goal requires strict adherence to standardized protocols for biomarker validation to ensure their integration into evidence-based clinical workflows. Current research should prioritize the development of clinically applicable biomarker assessment frameworks, particularly focusing on point-of-care testing (POCT), which remains at an early stage in the field of periodontology. Progress in this area is hindered by the lack of fully validated biomarkers for diagnostic use, limiting the practical application of biomarker-based analysis in precision diagnostics. Therefore, there is a critical need to identify and evaluate the most disease-specific and patient-relevant biomarkers to advance the implementation of precision periodontics into routine clinical practice.

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