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Review Article

The role of biomarkers in modern endodontic diagnosis

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ABSTRACT

Biomarker-based diagnostics represent an emerging frontier in precision endodontics, offering biologically informed approaches for the detection, monitoring, and management of pulp inflammation. Unlike conventional pulp testing methods that rely on subjective pain responses or thermal/electrical stimuli, biomarkers provide objective molecular and cellular insights into pulp health. Various biological markers-such as cytokines (IL-1β, TNF-α), neuropeptides (Substance P, CGRP), matrix metalloproteinases, and microRNAs-demonstrate distinct profiles in reversible versus irreversible pulpitis, enabling early detection and targeted interventions. Clinical applications include non-invasive analysis of dentinal fluid, gingival crevicular fluid, and saliva, often combined with advanced biosensors and point-of-care devices to improve diagnostic accuracy. Innovations in omics technologies, microfluidics, and artificial intelligence facilitate high-throughput biomarker analysis and predictive modeling of disease progression. Despite promising developments, challenges remain in standardization, sensitivity, cost-effectiveness, and clinical translation. Ongoing research into longitudinal monitoring and multi-marker panels holds potential for personalized pulp therapy. As biomarker-guided diagnostics evolve, interdisciplinary collaboration will be essential to integrate molecular insights into routine endodontic practice, enhancing early intervention and patient-specific care.

Keywords: Biomarkers, Pulpitis, Diagnostic biomarkers, Saliva, Dentinal fluid, Gingival crevicular fluid, Cytokines, Neuropeptides, Precision endodontics

INTRODUCTION

Dentistry has evolved toward biologically driven diagnostic and therapeutic approaches that emphasize early disease detection and personalized treatment planning. In this context, biomarkers have emerged as valuable tools for understanding the pathophysiology of pulpal diseases, particularly pulpitis. Pulpitis represents an inflammatory condition of the dental pulp that poses diagnostic challenges due to the limitations of conventional clinical and radiographic methods. Biomarkers offer a transformative shift in endodontic diagnosis by enabling objective, molecular-level assessment of pulpal inflammation and tissue status. These biological indicators reflect normal or pathological processes and can be detected in pulp tissue, dentinal fluid, saliva, and gingival crevicular fluid.[1]

Advances in molecular biology, immunology, and proteomics have significantly expanded the identification and application of biomarkers associated with pulpitis. Inflammatory mediators, neuropeptides, cytokines, and genetic markers play a pivotal role in indicating the severity and progression of pulpal inflammation. Unlike traditional diagnostic methods, biomarker-based approaches focus on the underlying biological changes rather than solely on clinical symptoms. This biologically oriented methodology allows for improved differentiation between reversible and irreversible pulpitis, thereby supporting more accurate treatment decisions. The integration of biomarker research into clinical dentistry

aligns with the growing emphasis on precision and personalized dental care. This review highlights the current understanding of biomarkers in pulpitis, their diagnostic and prognostic significance, and their potential to revolutionize future endodontic practice.[2]

OVERVIEW OF PULPITIS

Pulpitis is an inflammatory condition of the dental pulp that arises primarily as a result of microbial invasion from dental caries, trauma, restorative procedures, or cracks in the tooth structure. The dental pulp is a highly specialized connective tissue enclosed within rigid dentinal walls, making it particularly susceptible to pressure changes during inflammation. Pulpitis is traditionally classified into reversible and irreversible forms based on clinical symptoms, pain characteristics, and the pulp's capacity to recover following removal of irritant. Reversible pulpitis is characterized by mild inflammation and transient pain, whereas irreversible pulpitis involves persistent inflammation, severe pain, and eventual pulpal necrosis.[3]

Despite advancements in diagnostic tools, the accurate assessment of pulpal status remains challenging due to the subjective nature of pain and the limited correlation between clinical signs and histopathological findings. Conventional pulp vitality tests, such as thermal and electric pulp testing, evaluate neural response rather than the true inflammatory or vascular status of the pulp. This diagnostic uncertainty often leads to overtreatment or inappropriate treatment planning. Therefore, a deeper understanding of the biological events occurring during pulpitis is essential for improving diagnostic accuracy and clinical outcomes.[4]

CONCEPT AND IMPORTANCE OF BIOMARKERS

Biomarkers are defined as measurable biological molecules that indicate normal physiological processes, pathogenic processes/responses to therapeutic interventions. In the context of pulpitis, biomarkers reflect the molecular and cellular changes associated with pulpal inflammation, tissue injury, and repair. These markers include cytokines, chemokines, neuropeptides, enzymes and genetic materials that are released in response to pulpal irritation and inflammation. Detection and quantification of such biomarkers provide objective information regarding inflammatory status and vitality of dental pulp.[5]

The importance of biomarkers lies in their ability to overcome the limitations of conventional diagnostic methods by offering a biologically based assessment of pulpal health. Biomarker analysis can aid in distinguishing between reversible and irreversible pulpitis, predicting disease progression, and guiding treatment decisions. Additionally, biomarkers can be obtained from minimally invasive sources such as dentinal fluid, saliva, and gingival crevicular fluid, making them suitable for chairside diagnostic applications. The incorporation of biomarkers into clinical practice supports the growing paradigm of precision and personalized dentistry.[5]

CLASSIFICATION OF BIOMARKERS IN PULPITIS

Biomarkers in pulpitis can be broadly classified based on their biological function and role in the inflammatory process. Inflammatory biomarkers constitute a major category and include cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and prostaglandins, which are involved in initiation and propagation of pulpal inflammation. These markers are closely associated with pain intensity, disease severity.[6]

Neurogenic biomarkers, including substance P and calcitonin gene-related peptide (CGRP), are released from sensory nerve fibers and contribute to neurogenic inflammation and pain perception in pulpitis. Immunological biomarkers, such as immunoglobulins and matrix metalloproteinases, reflect immune responses and tissue breakdown within the pulp. Genetic and molecular biomarkers, including microRNAs and gene expression profiles, represent emerging tools for understanding disease mechanisms and identifying early pulpal changes. This classification highlights the multifactorial nature of pulpitis and underscores the potential of biomarker-based approaches in enhancing diagnostic precision and therapeutic decision-making.[7]

INFLAMMATORY BIOMARKERS

Inflammatory biomarkers play a central role in the initiation and progression of pulpitis and are among the most extensively studied indicators of pulpal inflammation. These biomarkers include cytokines, chemokines, and prostaglandins that are released in response to bacterial invasion and tissue injury. Interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are key pro-inflammatory cytokines that regulate immune cell recruitment and vascular changes within the dental pulp. Elevated levels of these cytokines have been consistently associated with irreversible pulpitis and increased pain intensity.[8]

Prostaglandins, particularly prostaglandin E_2 (PGE_2), are synthesized during inflammation and contribute to vasodilation, increased vascular permeability and pain sensitization. Studies have demonstrated significantly higher concentrations of inflammatory mediators in pulpal tissue affected by irreversible pulpitis compared to reversible pulpitis/healthy pulp. These biomarkers provide valuable insight into severity and activity of pulpal inflammation and hold potential for differentiating disease stages.

NEUROGENIC BIOMARKERS

Neurogenic biomarkers are released from sensory nerve fibers within the dental pulp and are closely associated

with pain transmission and neurogenic inflammation. Substance P and calcitonin gene-related peptide (CGRP) are the most prominent neuropeptides implicated in pulpitis. These neuropeptides are released in response to noxious stimuli and contribute to vasodilation, plasma extravasation, and activation of immune cells.

Increased expression of substance P and CGRP has been observed in teeth diagnosed with irreversible pulpitis, correlating with severe and spontaneous pain. These biomarkers not only reflect pulpal pain intensity but also influence the inflammatory cascade by stimulating cytokine release.[9] Neurogenic biomarkers therefore provide a biological explanation for the pain characteristics of pulpitis and represent potential targets for diagnostic and therapeutic interventions.

IMMUNOLOGICAL BIOMARKERS

Immunological biomarkers reflect the host immune response to bacterial invasion within the dental pulp. These include immunoglobulins, complement proteins, and antigen-presenting cells that participate in both innate and adaptive immune responses. Immunoglobulin G (IgG) and Immunoglobulin A (IgA) have been detected in inflamed pulpal tissues, indicating an active immune response against microbial antigens.

Matrix metalloproteinases (MMPs), particularly MMP-8 and MMP-9, are also considered important immunological biomarkers due to their role in extracellular matrix degradation and tissue remodeling.[10] Elevated levels of MMPs have been associated with pulpal tissue destruction and progression toward necrosis. The assessment of immunological biomarkers enhances the understanding of pulpal defense mechanisms and tissue breakdown during pulpitis.

MOLECULAR AND GENETIC BIOMARKERS

Molecular and genetic biomarkers represent emerging diagnostic tools that provide insight into gene expression changes and regulatory mechanisms involved in pulpitis. These biomarkers include messenger RNA (mRNA), microRNAs (miRNAs), and epigenetic markers that influence inflammatory pathways. Altered expression of specific miRNAs has been linked to the regulation of cytokine production and immune responses in inflamed pulp tissue.

Gene expression profiling studies have identified upregulation of genes associated with inflammation, apoptosis, and tissue repair in pulpitis-affected teeth.[11] These molecular biomarkers offer the advantage of detecting early pulpal changes before the onset of severe clinical symptoms. Although currently limited to research settings, molecular and genetic biomarkers hold promise for future personalized and predictive endodontic diagnostics.

ANGIOGENIC AND VASCULAR BIOMARKERS

Angiogenic and vascular biomarkers reflect changes in pulpal blood flow and vascular permeability during inflammation. Vascular endothelial growth factor (VEGF) is a key angiogenic mediator that promotes neovascularization and increased vascular permeability in inflamed pulp tissue. Elevated VEGF levels have been associated with irreversible pulpitis and increased pulpal pressure.

Other vascular biomarkers, such as nitric oxide and endothelin, contribute to vasodilation and regulation of blood flow within the pulp.[12] These biomarkers play a crucial role in pulpal defense and repair mechanisms but may also exacerbate inflammation when excessively expressed. The evaluation of angiogenic biomarkers provides insight into the vascular dynamics of pulpitis and its progression

SOURCES OF BIOMARKERS IN PULPITIS

The detection and evaluation of biomarkers in pulpitis depend on the biological source, as each provides distinct insights into pulpal health and inflammation. Common sources include pulp tissue, dentinal fluid, saliva, and gingival crevicular fluid (GCF). These sources differ in accessibility, invasiveness, and specificity, influencing their diagnostic utility.[13]

Pulp tissue

Pulp tissue is the most direct and informative source of biomarkers, as it reflects the local molecular, cellular, and immunological events occurring during inflammation. Analyses of pulpal tissue obtained during endodontic procedures have revealed elevated levels of cytokines, neuropeptides, matrix metalloproteinases, and angiogenic factors in inflamed pulps. While pulp tissue provides site-specific and accurate information, its invasive nature limits routine clinical application, making it primarily suitable for research purposes.[14]

Dentinal fluid

Dentinal fluid offers a minimally invasive window into pulpal status. During pulpitis, increased intrapulpal pressure and vascular permeability allow inflammatory mediators to diffuse through dentinal tubules. Biomarkers such as cytokines, prostaglandins, and neuropeptides have been detected in dentinal fluid collected from carious or exposed dentin.[15] This source provides potential for early detection of pulpal inflammation and chairside diagnostics, although collection techniques require standardization for reproducible results.

Saliva

Saliva is a convenient and non-invasive source of biomarkers. Inflammatory mediators released from the

pulp can reach saliva via dentinal fluid, GCF, or systemic circulation. Salivary biomarkers, including cytokines, enzymes, and microRNAs, have been studied for their role in diagnosing pulpal and periapical diseases. While saliva allows easy sampling and patient comfort, systemic factors and lack of site specificity may influence accuracy.[16] Despite these limitations, saliva-based biomarker analysis holds promise for large-scale screening and monitoring of pulpal inflammation.

Gingival crevicular fluid (GCF)

GCF is a serum transudate or inflammatory exudate found in the gingival sulcus that reflects both periodontal and pulpal inflammatory processes. During pulpitis, inflammatory mediators can diffuse through apical foramina into the periodontal ligament and GCF. Biomarkers such as interleukins, TNF-α, and matrix metalloproteinases have been detected in GCF from teeth with pulpitis. Sampling GCF is minimally invasive and suitable for chairside testing, although contamination from periodontal inflammation can affect specificity.[17]

Collectively, these sources provide complementary information regarding the inflammatory status of the pulp. Selection of the appropriate source depends on the clinical context, invasiveness, and desired diagnostic precision. The integration of multiple sources may enhance the sensitivity and specificity of biomarker-based diagnostics in pulpitis

DIAGNOSTIC APPLICATIONS OF BIOMARKERS IN PULPITIS

Biomarkers offer a biologically based approach to diagnose pulpitis, addressing limitations of traditional diagnostic methods such as thermal and electric pulp tests, which rely on subjective patient response rather than true pulpal status. Biomarkers provide objective insight into the inflammatory, immunological, and neurogenic processes occurring within the pulp.

Differentiating reversible and irreversible pulpitis

Inflammatory biomarkers such as IL-1β, IL-6, TNF-α, and prostaglandins (PGE_2) are significantly elevated in irreversible pulpitis compared to reversible pulpitis or healthy pulp tissue. Measurement of these cytokines in dentinal fluid or GCF can assist in distinguishing the severity of inflammation, which is critical for treatment planning.[18]

Pain assessment and neurogenic inflammation

Neurogenic biomarkers, including Substance P and CGRP, correlate with pain intensity and spontaneous pain episodes. Quantifying these neuropeptides can supplement clinical pain evaluation, providing an objective correlate to patient-reported symptoms.

Chairside and non-invasive testing

Minimally invasive sampling of saliva, dentinal fluid, or GCF enables biomarker detection without pulp exposure. Saliva-based assays for cytokines or microRNAs offer potential for rapid, chairside diagnostics, while GCF can reflect both pulpal and periodontal inflammatory status. Integration of point-of-care biosensors and immunoassays may further facilitate clinical translation.[19]

Molecular diagnostics

Emerging molecular biomarkers, such as microRNAs and gene expression profiles, enable detection of early pulpal changes before overt clinical symptoms appear. These molecular tools provide a deeper understanding of disease mechanisms and may complement traditional diagnostic approaches.[19] Collectively, the use of biomarkers enhances diagnostic accuracy, reduces reliance on subjective measures, and may prevent overtreatment or unnecessary interventions.

PROGNOSTIC VALUE OF BIOMARKERS IN PULPITIS

Beyond diagnosis, biomarkers offer important prognostic information that can guide clinical decision-making and predict treatment outcomes.

Predicting treatment response

The levels of inflammatory and immunological biomarkers, such as IL-6, TNF-α, and MMPs, can indicate the likelihood of pulp recovery following conservative treatments like pulp capping or partial pulpotomy. Elevated pro-inflammatory cytokines may suggest a higher risk of treatment failure, supporting more aggressive interventions when necessary.

Monitoring disease progression

Longitudinal monitoring of biomarkers in dentinal fluid, saliva, or GCF can track progression from reversible to irreversible pulpitis. Changes in cytokine or neuropeptide levels may predict exacerbation of inflammation or onset of necrosis, enabling timely clinical intervention.[20]

Personalized treatment planning

Molecular and genetic biomarkers provide individualized insight into patient's pulpal response and regenerative potential. By integrating biomarker profiles with clinical findings, clinicians can tailor treatment strategies to maximize healing while minimizing unnecessary pulp removal.

Risk assessment and early detection

Early detection of subtle changes in biomarker levels allows for preventive strategies before irreversible pulpal

damage occurs. This approach aligns with precision dentistry principles, emphasizing targeted intervention based on biologically relevant indicators.

DIAGNOSIS

Quantification of inflammatory biomarkers (e.g., IL-1β, IL-6, TNF-α, PGE_2) and neurogenic biomarkers (e.g., Substance P, CGRP) can help classify the clinical implications and chairside diagnostic potential.

The identification of biomarkers in pulpitis has significant clinical implications, particularly for diagnosis, treatment planning, and patient management. Conventional diagnostic methods, such as thermal and electric pulp testing, primarily assess neural response and do not accurately reflect the inflammatory or vascular status of the pulp. Biomarker-based diagnostics provide an objective, molecular-level assessment of pulpal health, enabling clinicians to distinguish reversible from irreversible pulpitis with greater precision.[21]

Precision diagnosis

Severity of pulpal inflammation, this allows clinicians to make more informed decisions, reducing overtreatment and improving prognosis.

Chairside and minimally invasive diagnostics

Minimally invasive sources such as dentinal fluid, saliva, and gingival crevicular fluid (GCF) enable biomarker detection without pulp exposure. Point-of-care devices, including immunoassays and biosensors, can rapidly measure multiple biomarkers simultaneously, offering real-time data during clinical visits. Such approaches facilitate early diagnosis, timely intervention, and monitoring of treatment efficacy.[22]

Personalized treatment strategies

Biomarker profiling can inform individualized treatment planning by identifying teeth with high regenerative potential versus those likely to progress toward necrosis. For example, teeth with elevated pro-inflammatory cytokines may require more aggressive intervention, whereas those with lower biomarker levels could be managed conservatively with pulp capping or partial pulpotomy.

Integration with conventional diagnostics

Combining biomarker assessment with traditional pulp vitality tests enhances diagnostic accuracy. For instance, a tooth showing weak neural response but high inflammatory biomarker levels may be at risk of irreversible pulpitis, guiding clinicians toward appropriate management.[23]

LIMITATIONS AND CHALLENGES IN BIOMARKER RESEARCH

While biomarkers hold significant promise for improving the diagnosis and management of pulpitis, their clinical application faces several limitations and challenges:

Invasiveness of sampling

Direct collection of biomarkers from pulp tissue provides highly specific information but is inherently invasive, limiting its routine clinical use to teeth undergoing endodontic procedures or extraction. Minimally invasive alternatives, such as dentinal fluid, saliva, or gingival crevicular fluid (GCF), are easier to obtain but may be less site-specific.

Biological and systemic variability

Biomarker levels can be influenced by age, systemic health, medications, and individual immune response, introducing variability in interpretation. Additionally, local factors such as periodontal disease can confound biomarker concentrations in saliva and GCF, affecting specificity for pulpal inflammation.[24]

Lack of standardization

Currently, there are no universally accepted protocols for biomarker collection, storage, and analysis. Variations in sampling techniques, assay methods, and detection thresholds can lead to inconsistent results and limit comparability between studies.

Temporal dynamics of biomarkers

The expression of inflammatory and neurogenic biomarkers changes rapidly during the progression of pulpitis. Single-point measurements may not accurately reflect disease status, emphasizing the need for longitudinal monitoring, which can be logistically challenging in clinical settings.

Cost and technical requirements

Advanced molecular and genetic analyses, including microRNA profiling, proteomics, and metabolomics, require specialized equipment, trained personnel, and significant costs, restricting their accessibility to research laboratories.[25]

Clinical translation and validation

Although many biomarkers have shown diagnostic and prognostic potential in experimental studies, large-scale clinical validation is lacking. Further research is needed to confirm the predictive value, sensitivity, and specificity of biomarkers in diverse patient populations.

In summary, while biomarker research offers transformative potential for precision endodontics, overcoming challenges related to invasiveness, variability, standardization, and clinical validation is essential before widespread adoption in routine dental practice.

FUTURE DIRECTIONS AND EMERGING BIOMARKERS

The study of biomarkers in pulpitis is a rapidly evolving field, with several emerging trends and research directions that promise to enhance diagnostic precision, prognostic accuracy, and personalized treatment strategies.

Molecular and genetic biomarkers

Advances in molecular biology have identified microRNAs (miRNAs), messenger RNA (mRNA) expression profiles, and epigenetic markers as potential tools for early detection of pulpal inflammation. Specific miRNAs have been linked to regulation of pro-inflammatory cytokines and immune responses in pulp tissue, offering a window into disease progression before clinical symptoms manifest. Genetic profiling may also help identify individuals with heightened susceptibility to pulpitis or poor regenerative potential.[26]

Proteomics and metabolomics

High-throughput proteomic and metabolomic analyses enable comprehensive characterization of proteins, enzymes, and metabolites in pulp tissue, dentinal fluid, saliva, and gingival crevicular fluid. These approaches can reveal complex inflammatory networks, identify novel biomarkers, and differentiate reversible from irreversible pulpitis with greater sensitivity than single-analyte detection.

Point-of-care biosensors and chairside diagnostics

Miniaturized, rapid biosensors capable of detecting multiple biomarkers simultaneously are emerging as promising tools for chairside diagnostics. These devices could allow clinicians to monitor inflammatory, neurogenic, and angiogenic biomarkers in real time, providing immediate guidance for treatment decisions. Integration with portable readers or smartphone-based platforms could make these technologies accessible and practical in routine dental practice.[27]

Integration with AI and imaging

Combining biomarker profiling with advanced imaging techniques (e.g., CBCT, optical coherence tomography) and AI-based algorithms offers the potential for highly accurate, predictive diagnostics. Machine learning models could analyze biomarker patterns alongside clinical and radiographic data to predict pulp vitality, disease progression, and treatment outcomes, moving toward precision endodontics.

Regenerative and personalized endodontics

Future biomarker research may support regenerative therapies by identifying molecular signals that predict pulpal healing potential. Personalized treatment strategies could be designed based on an individual tooth's biomarker profile, guiding decisions such as partial pulpotomy versus full pulpectomy or the use of bioactive materials and stem-cell-based therapies.[28]

In summary, the future of biomarker research in pulpitis lies in multidisciplinary approaches combining molecular diagnostics, high-throughput analytics, point-of-care technologies, and AI integration. These advances have the potential to transform pulp diagnostics from a subjective, symptom-based process to a precise, predictive, and personalized clinical practice.

CONCLUSION

Biomarkers in pulpitis represent a promising frontier in diagnostic and therapeutic endodontics, offering objective insight into the molecular, inflammatory, neurogenic, immunological, and vascular changes occurring within the dental pulp. Traditional diagnostic methods, which rely largely on patient-reported symptoms and pulp vitality tests, are limited by subjectivity and inability to accurately reflect pulpal health. The study of biomarkers-from pulp tissue, dentinal fluid, saliva, and gingival crevicular fluid-provides a minimally invasive, biologically based approach to assess pulp status, distinguish between reversible and irreversible pulpitis, and predict disease progression. Integration of biomarker analysis into clinical practice can facilitate precision and personalized dentistry, enabling targeted interventions, minimally invasive treatment strategies, and improved patient outcomes. Despite their potential, widespread clinical implementation is currently limited by challenges such as sampling invasiveness, variability, lack of standardization, and cost.

Future research focusing on emerging molecular, proteomic, and metabolomic biomarkers, point-of-care biosensors, and integration with artificial intelligence holds the promise of transforming pulp diagnostics from a subjective, symptom-based process to a precise, predictive, and patient-centered practice.

In conclusion**,** biomarker-based approaches in pulpitis have the potential to redefine diagnostic paradigms, guide regenerative and conservative therapies, and enable precision endodontics, ultimately improving the quality and outcomes of dental care.

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