Volume 10, Issue 7, July – 2025 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul1894

Endodontic Biomarkers: A Paradigm Shift in Endodontic Diagnosis

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Publication Date: 2025/08/16

Abstract: For evaluating the accuracy of vital pulp therapy for an inflamed pulp, the use of non-invasive diagnostic tools are essential to avoid further damage to the pulp dentin complex. The identification of specific biomarkers reflecting the inflammatory status of the dental pulp holds significant promise in guiding accurate diagnosis and enabling personalized treatment strategies. This review article focuses upon delivering brief information on endodontic biomarkers seen in different pulpal and peri apical pathologies and their isolation techniques.

Keywords: *Endodontic Biomarkers, Periapical Inflammation, Apical Periodontitis, Diagnostic Test.*

How to Cite: Dr. K Shreya Shetty; Dr. Swathi Amin (2025) Endodontic Biomarkers: A Paradigm Shift in Endodontic Diagnosis. *International Journal of Innovative Science and Research Technology*, 10(7), 3588-3594. https://doi.org/10.38124/ijisrt/25jul1894

I. INTRODUCTION

Dental caries is the most common disease which affects the enamel and its supporting structures, if it is untreated it will lead to pulpal and peri apical inflammation. This inflammation can be due to trauma, infection of supporting structure of tooth, chemical injuries, bacterial infections. Presently, diagnostic procedures for assessing pulpal inflammation rely on case history, along with clinical and radiographic examinations. Clinical evaluation includes techniques such as visual inspection, assessment of pulp sensitivity to thermal or electric stimuli, and evaluation of pain on palpation or percussion. Notably, these diagnostic approaches have remained largely unchanged over the past decade. However, the accuracy and validity of these conventional clinical tests in reflecting the actual histopathological status of the pulp remain a subject of ongoing debate.[1]

A recent literature review summarized the available data on the diagnostic accuracy of clinical signs, symptoms, and currently used tests to assess pulpal condition.[1] The authors concluded that the overall evidence remains insufficient to support the accuracy of these tests, even when used in combination. Consequently, current diagnostic procedures do not reliably reflect the true inflammatory status of the dental pulp.

Molecular and cellular biology play vital role in understanding the pathophysiology of these diseases and coming to accurate diagnosis and treatment plan. Inflamed pulp is characterized by an increased number of inflammatory cells and the elevated production of mediators such as proteases, chemokines, growth factors, and cytokines, all of which contribute to the amplification of the immune response [2]. Biomarkers serve as an important parameter which indicates the physiology and health of a tissue which can be measurable and quantifiable. Bence -jones protein which is mono clonal immunoglobulin first biomarker which is isolated in patients suffering from multiple myeloma.[1]

Accurate assessment of pulpal inflammation is critical when deciding whether to preserve the pulp through procedures such as direct or indirect pulp capping, or to proceed with more invasive treatments like root canal therapy. This decision largely depends on the clinician's ability to distinguish between the different stages of pulpal inflammation. [3] Notably, the inflammatory mediators involved may serve as potential biomarkers, offering a more precise and objective tool for endodontic diagnosis.[4]

The National Institutes of Health (NIH) defines a biomarker as a 'characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [5] Molecules involved in the inflammatory cascade may serve as diagnostic biomarkers, indicating the presence and degree of tissue inflammation. Emerging research suggests that the dental pulp is not merely an isolated structure confined within rigid dentin walls, but rather a dynamic and reactive tissue capable of releasing biological products into its surrounding environment.[1]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul1894

Biomarkers can be considered indicators of molecular interactions occurring at functional, physiological, biochemical, or cellular levels. They are widely utilized in both research and clinical settings to aid in diagnosis and guide treatment decisions. This review article aims to provide an overview of the biomarkers associated with pulpal and periapical diseases, as well as the methods used for their isolation.

➢ *Role of Inflammatory Biomarkers in Endodontics:*

Arriving at proper diagnosis in management of pulpitis is complex and tough process. Choice of treatment between deep caries management and endodontic therapy mainly depends on stages of pulpal inflammation. Since conventional diagnostic methods will not provide any information regarding the histological status of pulp, molecular diagnosis has to play a major role in accurate diagnosis and treatment planning of peri radicular and pulpal pathosis. Numerous events take place at microscopic and cellular level in response to pulpal inflammation. The main inflammatory mediators released during event are cytokines, protease, growth factors. Qualitative and quantitative assessment of these mediators is very important in recognizing the stages of inflammation in relation to nature of immune response produced in the tissue. Few mediators are released during tissue inflammation while others during tissue regeneration. Thus, identifying these mediators will provide the information regarding accurate stages of inflammation which helps to precise diagnosis and treatment plan.

Immunocompetent tissues in the dental pulp exhibit a characteristic response during pulpitis, marked by the release of inflammatory mediators that initiate a cascade of events including inflammation and attempts at tissue repair.[1] Research indicates that these pathological events can be assessed through quantifiable levels of specific biomarkers, which correlate with the inflammatory status. These biomarkers can be detected in biological fluids such as pulpal blood, periapical fluid, dentinal fluid, and gingival crevicular fluid. [6-8]

Endodontic infections, such as apical periodontitis, have been shown to influence the levels of various inflammatory markers. These include high-sensitivity C-reactive protein (hs-CRP), interleukins (IL-1, IL-6, IL-10, IL-12), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMP-8 and MMP-9), all of which play critical roles in the host immune response and tissue degradation.[9]

A histological study by Garrido et al. reported elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP) messenger ribonucleic acid (mRNA) in the periodontal ligament tissue of teeth affected by apical periodontitis.[10]

Matrix metalloproteinases, such as MMP-9 and MMP-13, which are involved in cell death and extracellular matrix degradation, can be considered potential biomarkers of pulpal inflammation.[11] Fibroblast growth factors, Vascular endothelial growth factors (VEGF) seen in pulpal tissue samples of reversible pulpitis.[12] This suggests, bio markers also seen in healing tissue indicate tissue repair.

➢ *Isolation of Biomarker Molecules:*

The biomarkers can be isolated from various fluids in the body like pulpal blood, gingival crevicular fluid, peri apical fluid. This can be collected non-invasively and evaluated for various diagnostic purpose.

- *Pulpal Blood:*

Pulpal blood refers to blood supply with in the pulp it may contain factors which is different from peripheral blood in the context of inflammation and diseases. This can be collected directly from pulp tissue making them more invasive. This may jeopardize the normal pulpal physiology.

- *Periapical Fluid:*

This is an interstitial fluid surrounding the root tip of tooth, contains various bio markers that provide valuable insights about apical periodontitis. It contains pro and anti-inflammatory (autocrine and paracrine) mediators which coordinate various cellular activities associated with tissue damage and onset of clinical symptoms.[13] The sample of peri apical fluid is taken using paper point through the root canal. Several studies have demonstrated that these biological fluids can be collected for local biomarker molecular analysis, providing proof-of-concept for their potential use in diagnostic, prognostic, and predictive applications.[13] But this sampling technique is invasive because it needs complete extirpation of pulp tissue in the root canal. Thus, a non-invasive chairside sampling technique focusing individual or group of analytes could provide clinician with more vital information regarding the peri radicular diseases status than conventional diagnostic methods.

- *Dentinal Fluid (DF):*

It is an extracellular liquid present inside the dentinal tubule contains molecules which is related to inflammation. These inflammatory markers provide valuable information which helps clinicians to distinguish among symptomatic irreversible pulpitis and reversible pulpitis. It has been reported that dentinal fluid (DF) may be utilized as a patient-specific diagnostic medium for pulp disease. Additionally, it holds potential as a liquid biopsy tool to assess the concentration of various constituents present in pulpal tissue fluid. [14] Although these indicators have potential diagnostic value, collecting dentinal fluid is invasive since it requires removal of restorations and dentine.

- *Gingival Crevicular Fluid (GCF):*

Gingival crevicular fluid (GCF) is an inflammatory exudate produced from the gingival plexus of blood vessels in the gingival corium, next to the epithelium lining of the dentogingival space. It can be obtained non-invasively from the gingival sulcus and contains potential bio markers which provide valuable information regarding periodontal diseases. Bostanci and colleagues conducted a quantitative proteomic analysis of gingival crevicular fluid (GCF) samples from five healthy individuals and five patients with aggressive periodontitis. Their findings revealed that proteins such as cystatin-B and defensins were detected exclusively in the healthy control group, whereas L-plastin was identified only in the samples from patients with aggressive periodontitis [15].

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The other bio markers which present in the GCF are cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) as well as matrix metalloproteinases (MMPs) like MMP-8 and MMP-9.[16]

- *Saliva:*

Saliva is an exocrine secretion of the salivary glands which reflects the both oral and systemic health status. Furthermore, it can be collected non-invasively and analysed for bio markers for diagnosing the chronic diseases and to allow a continuous disease monitoring. The commonly seen bio markers in saliva are IL1, TNF, IL6 and C- reactive protein especially during periodontal destruction. Cytokines, salivary levels of IL1, IL4, IL6, IL8 and tumour necrosis factor (TNF), have been labelled as pertinent biomarkers for oral lichen planus diagnosis and prognosis [17].

➢ *Bio Markers in Endodontics:*

Various types of biomarkers can be separated from various types fluids, saliva, blood, dental tissues and gingival crevicular fluid [18].

- Inflammatory Bio markers: They are produced in response to endodontic infections like TNF Alpha, Prostaglandins (PGE2), IL 1, IL 6, IL 8 etc
- Tissue destruction Biomarkers: The bio markers indicate tissue destructions due to chronic infection, inflammation. Eg: Matrix metalloproteinases (MMPs), Deoxypyridinoline (DPD)
- Microbial Bio markers: These are produced in response to specific infections. Eg:, Endotoxins released by the bacteria, Bacterial DNA or RNA.
- Regenerative Bio Markers: They indicate tissue repair or regeneration. Eg: Growth factors, Bone morphogenic proteins (BMPs)

Table 1 Biomarkers of Diseases of Pulp and Periapical Tissue [19]

Disease	Sl. no	Biomarker	Role
Caries	1	Matrix Metalloproteinases (MMP)	Derived from host cells participate in the destruction of dentin after bacterial acid demineralization
	2	Alkaline Phosphatase (ALP)	Repair and healing after pulpal injury
Reversible pulpitis	1	Prostaglandin E2	Multiple pro -inflammatory immunomodulatory properties
	2	Interleukin 1 beta (IL -1 beta)	Regulates immune and inflammatory reactions, stimulates bone resorption
	3	Osteocalcin	Regulation of bone mineralization
Irreversible pulpitis	1	Substance P	Vasoactive mediator, immune mediator
	2	Matrix metalloproteinase - 3 (MMP-3)	Hydrolysis of intercellular matrix
Asymptomatic Apical Periodontitis	1	RANKL and osteoprogerin (OPG)	Promotes dendritic cell survival, induces osteoclastic differentiation from hemopoietic precursors leading to bone resorption
	2	MMP-2 (Gelatinase)	Hydrolysis of intercellular matrix
Chronic periodontitis	1	MMP-8	Degradation of collagen type 1,2 and 3
Periapical abscess	1	Mesenchymal stem cells (MSCs)	Tissue repair and regeneration
	2	8- Isoprostane	Biological activity as inflammatory mediators that augments pain perception
Periapical cyst	1	Cytokines (IL-6)	Regulator of T and B cell growth, acute phase protein production

➢ *Matrix Metalloproteinases (MMPs):*

These are secreted by connective tissues like fibroblast, osteoblast and odontoblast and secreted into extra cellular matrix and has vital role in primary and reparative dentin formation, modulation of dental caries progression. It is seen that matrix metalloproteinases (MMPs), such as MMP-2, MMP-8, and MMP-9, play a important role in various dental diseases [19]. Although their levels are low in sound pulpal tissue, but it will increase in pathological conditions. Polymerase chain reaction (PCR) and immunohistochemistry techniques usually used to identify this bio markers from pulp dentin complex.

➢ *Matrix Metalloproteinase – 3 (MMP-3):*

Their levels are increased in reversible pulpitis and they promote collagen destruction, reparative dentin formation, angiogenesis. [20]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul1894

➢ *Matrix Metalloproteinase-8 (MMP-8 / Collagenases):*

Play major role in caries modulation and dentinogenesis. Aguirre-López EC et al, showed that MMP-8 levels are elevated less in the case of reversible pulpitis than in irreversible pulpitis. [21]

➢ *Matrix Metalloproteinase - 9 (MMP-9):*

It is major MMPs which play major role in breakdown of pulp tissue. Its level increase in symptomatic irreversible pulpitis. Studies have shown that the level of matrix metalloproteinase-9 (MMP-9) can serve as a potential biomarker for pulpal diagnosis and may also act as a predictor for the clinical outcome of pulpotomy procedures. [22]

➢ *Tumour Necrosis Factor – Alpha (TNF Alpha):*

It is cytokine which is intricate in acute phase of inflammation mainly produced by macrophages, CD4 lymphocytes, mast cells and neutrophils. It controls the inflammation and recruiting the immune cells to sites of injury.[19]

➢ *Vascular endothelial growth factor (VEGF):*

It is protein which stimulate the blood vessel formation**.** It has crucial role in wound healing, vascular permeability and homeostasis.

➢ *Substance P:*

It is a neuro transmitter has key role transmission of pain during pulpal inflammation.

Substance P also plays roles in wound healing, angiogenesis, and the regulation of respiratory and cardiovascular function. [19]

➢ *Manganese Superoxide Dismutases (Mn-SODs):*

It is found in mitochondrial matrix of cells formed by incomplete oxygen reduction.These molecules are released during inflammatory process by host cells[19]

➢ *Calcitonin Gene-Related Peptide (CGRP):*

It is neuro peptide secreted by the unmyelinated C fibres contribute to vascular, inflammatory and necrotic inflammation. Abd-Elmeguid A et al conducted a study that evalauted that concentration of OCN is higher in reversible pulpitis than changes in pulpal tissue[23]. It has two variants namely alpha-CGRP and beta-CGRP, also known as CGRP I and CGRP II.

➢ *Osteocalcin (OCN):*

It is reparative bio marker secreted during reactionary dentinogenesis by osteo blast and odontoblast in response to the pulp in irreversible pulpitis, signifying its great role in dental pulp repair.[23]

➢ *Interleukins (IL):*

It is group of cytokines produced by immune cells i.e leucocytes, mediate inflammatory events between the cells like proliferation, differentiation, cell requirement, apoptosis and etc. During pulpal inflammation IL levels increase which stimulate the secretion of MMPs which in turn result in pulpal extra cellular matrix degradation. IL-1α s is seen during both in reversible and irreversible pulpitis.[24] Increased levels of IL-2 is observed in asymptomatic deep caries activity or mild inflamed pulp tissue. [25]

➢ *Substance- P:*

It is neuro peptide secreted in response to neurogenic inflammation from free nerve endings by neutrophils and mast cells. It plays a major role in blood flow modulation during pulpal inflammation and tissue repair and is elevated during irreversible pulpitis.

➢ *RANKL and Osteoprogerin (OPG):*

These two molecules which control the bone metabolism i.e. bone resorption and bone deposition usually seen in apical periodontal tissues. Their levels are remarkably increased in both symptomatic and asymptomatic apical periodontitis. The ratio between Rankl and OPG gives a clear indication of progression and stage of apical periodontitis.[26] Root resorption following orthodontic tooth movement and traumatic injuries is associated with rise in these molecules.[26]

➢ *Tartrate-Resistant Acid Phosphatase (TRAP):*

This bio marker released by osteoclast responsible for bone resorption in peri apical and peri radicular tissue. Their levels indicate progression and level of bone destruction in apical periodontitis.

➢ *Deoxypyridinoline (DPD):*

It is also called Pyrilinks-D or deoxyPYD released into blood stream and urine indicated bone resorption and collagen matrix break down. Higher levels of DPD are related with bone resorption, mainly in conditions such as severe periapical lesions.[26]

➢ *microRNS (miRNAs):*

These are single stranded RNA molecules predominantly serve as bio markers of cancer and auto immune diseases. These are isolated from GCF of patients with orthodontic induced root resorption.[27]

➢ *Dentin Sialophosphoprotein (DSPP):*

These are dentin specific non collagenase proteins released by the pulp into dentinal matrix associated with bone resorption. It can be isolated from GCF of patients with orthodontic induced root resorption.[27]

➢ *C Reactive Protein (CRP):*

This protein produced by liver in response to inflammation elevated during periapical lesions and apical periodontitis.

➢ *Forkhead Box P3 (FoxP3) Transcription Factor:*

It is main master regulator of T regulatory cells (Treg cells), maintains association between anti-inflammatory responses and host's inflammatory. The no of Treg cells more in chronic periapical lesions than acute lesions.[28]

➢ *Mesenchymal Stem Cell Marker (MSCs):*

These cells play major role in development of periapical granuloma and periapical cyst. Cysts and granulomas are

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul1894

inflammatory response of peri apical tissues to infection. MSCs are usually in patients with periapical cyst and granuloma and act as potential bio marker candidates [29]

II. IN OFFICE TESTS

The tests which used to diagnose the bio markers should be simple, rapid, affordable and give predictable results.

➢ *Lateral Flow Essays:*

Lateral flow tests are one of the maximum significant types of paper-based point-of-care (POCT) diagnostic tools. They offer simple point of care testing used to assess pulpal vitality, monitor the progression of inflammation, and aid in the diagnosis of apical periodontitis. [29] The test requires only a small sample volume (5 μL) combined with a buffer, allowing the sample to flow along a solid phase that contains Platelet Factor 4 (PF4) complexed with a polyanion at a specific location. The formation of a visible band indicates the presence of antibodies. Key advantages of this assay include its rapid turnaround time, lack of need for specialized equipment, and high sensitivity. However, limitations include its qualitative nature—based on visual inspection rather than quantification—potentially low inter-observer reproducibility in cases of weak antibody responses, and overly high sensitivity, which may lead to poor specificity overal.[30]

➢ *Lab-on-a-Chip (LOC) Systems:*

Lab-on-a-Chip (LoC) systems refer to technologies that miniaturize and integrate multiple laboratory operations—such as chemical synthesis and analysis—onto a single microchip, resulting in a compact, handheld, and portable diagnostic device.[32] LoC devices are capable of scaling down single or multiple laboratory functions into a chip-format platform through the integration of microfluidics, electronics, optics, and biosensors. The primary objective of LoC technology is to facilitate advanced pathological analysis in a simplified and accessible format.[31] These systems have shown significant potential in the early-stage diagnosis of chronic and life-threatening diseases. Key advantages include high sensitivity, reduced human error, rapid results, portability, and low operational cost. In dentistry, LoC technology is primarily utilized for evaluating saliva to detect inflammatory cytokines, pathogens such as *Enterococcus faecalis*, and various viruses.[32]

➢ *Integrated Microfluidic Platform (IMPs):*

Integrated Microfluidic Platforms (IMPs) are diagnostic or analytical systems that incorporate microfluidic technologies to streamline multiple steps of medical diagnosis into a single, automated process.[33] A key feature of this approach is the ability to rapidly measure multiple analytes simultaneously. This multiplexing capability is particularly valuable in the early and accurate diagnosis of chronic inflammatory diseases, such as periodontitis, where assessing a comprehensive biomarker profile—or 'diagnostic signature'—offers greater diagnostic accuracy than evaluating individual biomarkers alone. [34]

This device is designed to evaluate salivary biomarkers as indicators of oral disease. Small volumes of saliva (approximately 10 mL) can be rapidly and hands-free analyzed for analyte concentrations and other biomarkers using electrophoretic immunoassays.[30] IMPS analysis of saliva for two cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) which have significant correlation with the progression of periodontal disease.[34]

➢ *Applications of Bio Markers in Endodontics:*

- Bio markers like IL-1, IL-6, TNF-α and prostaglandins are helps to distinguish clearly between reversible and irreversible pulpitis helps to execute proper treatment plan.[18]
- They help to diagnosing peri apical pathology and rate their severity which helps to proper treatment plan.[18]
- Bio markers help to evaluate the endodontic treatment out come by specifying the extent of infection.[18]
- To access the risk factors associated with endodontic infections.
- Early detection of pulpal and peri apical pathosis which will prevent more invasive treatment procedures.[18]
- Biomarkers in gingival crevicular fluid will be used to access the consequence of vital pulp therapy.[34]
- Bio markers can be used to evaluate the efficacy of treatment. By tracking the inflammatory and microbial markers during and after treatment it can be concluded that whether the infection is healing and if further treatment is needed. [18]

➢ *Challenges and Future Perspectives:*

For good reliability, consistency, there is need for systematic techniques to collect and evaluate the samples for bio markers. More studies are required for substantiate clinical utility of biomarkers. Advancements in techniques, for identification, quantification of bio markers such as proteomics, metabolomics and next- generation sequencing will play a crucial role in use of biomarkers in endodontics. [18] Amalgamation of routine diagnostic tests and analysis of biomarkers will improve the diagnosis and treatment planning. It requires development user friendly diagnostic kits in clinical practice.

III. CONCLUSION

For endodontists arriving at proper diagnosis, treatment plan only based on the clinical symptoms and diagnostic tests is challenging task. Combining endodontic biomarkers into routine endodontic practice carry the pivotal role in converting the field by aiding early and proper diagnosis, tailored treatment plan, and better treatment quality. But difficulties lie in collecting, analysing, interpretation of proper results must be over powered.

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