International Journal of Pathology and Biomarkers
https://ijpb.org/
IJP
SPBH

Review Article

Biomarkers for pulp and periapical Diagnosis Procedure

Ruaa Neamah Muslim[1], Ghadeer Shakir Shabaa[2], Wasan Abdulridha Hasan[3]

1. Department of Restorative and Aesthetic Dentistry College, Alkafeel University, Iraq
Email: ruaa.neamah@alkafeel.edu.iq
2. University of Alkafeel/College of Dentistry, Najaf, Iraq
Email: ghadeer.shakir@alkafeel.edu.iq
3. Al-Zahrawi University College of Dentistry, Karbala, Iraq
Email: wasan.abd@alzahu.edu.iq

Corresponding author: Ruaa Neamah Muslim
Department of Restorative and Aesthetic Dentistry College, Alkafeel University, Iraq
Email: ruaa.neamah@alkafeel.edu.iq

DOI: https://doi.org/10.71428/IJPB.2026.0105

1.1 Abstract

This study emphasizes biomarkers' ability to improve diagnostic precision and treatment outcomes for pulp and periapical disorders. Although effective, conventional diagnostic methods sometimes rely on subjective evaluations and may miss subtle illness changes. This study assesses pulpal and periapical disease biomarkers' clinical diagnostic value. To identify indicators of tooth pulp and periapical tissue inflammation and necrosis, recent literature was reviewed. Clinical trials assessing biomarker sensitivity and specificity were also assessed. Biomarkers can provide objective, quantitative information that, when paired with established diagnostic approaches, may help identify and treat pulp and periapical problems earlier.

Keywords: Periradicular area, Pulpitis, Acute pulpitis, biomarkers, diagnosis, inflammatory mediator.

1.2 Introduction

The tooth pulp, like other tissues, uses inflammation to suppress infections and start repair. Inflammation is needed to heal and regenerate the dentine pulp complex; otherwise, chronic disease or necrosis will occur. Predicting pulp clinical condition requires pulp inflammation severity assessment. The diagnostic limit is also described in situ inflammation [1]. Macroscopic, biological, and cellular methods are needed to assess pulp inflammation. Vasodilation is a noticeable vascular stage improvement. Increased immune cells are visible under a microscope. Multiple inflammatory biomolecules were released. It was also noticed that the dentin pulp complex creates and expels signaling molecules and cytokines before immune cell formation, suggesting that the cellular immunological response precedes it [2].

This diversity of mediators is important in inflammatory mediation, especially in relation to the host tissue's immunological response. Mediators accelerate inflammation. Thus, gathering such mediators could improve pulp condition assessments, diagnostic methods, and treatment outcomes [1].

1.3 Aim of this literature

The aims of this work were:

Received: March 5, 2025. Accepted: May 1, 2026. Published: June 1, 2026

1- To review the current literature knowledge regarding the inflammatory status of the pulp and periapical condition.
2- To summarize the available laboratory and clinically applicable procedures used in the determination of the inflammatory condition of the pulp and apical periodontal region.

2.1 Method

Search for articles was carried out on the internet for English articles published from 2000 to 2020, and included in vitro and clinical trial studies using these sites: PubMed, Google Scholar, and Research Gate. The search was carried out using the following terms; Periarticular area, Pulpitis, Acute pulpitis, biomarkers, diagnosis, and inflammatory mediator. The collected articles were carefully inspected to identify the relevant topics. In addition, the bibliography for the obtained articles was also examined, and the relevant references were included within the data base researches

2.2 Inflammatory conditions of the pulp

The American Academy of Endodontists' criteria classify pulpitis as reversible or irreversible [3]. Pulpitis is caused by opportunistic pulp cavity infection with oral bacteria. Most microorganisms enter through the dental cavities. Pulpal infections can also result from damage, dentinal cracks, inflammatory tubules, or the main apical foramen. Pulpal histologic and clinical categorization needs strengthening and elegance. Regular and dead pulps have similar histologic features, although transient and permanent pulpitis are uncertain. Reversible pulpitis has no microorganisms and limited aggregation and liquefaction necrosis around the irritant, according to histology. Other irreversible pulpitis has bacteria or their metabolites and trash in the tooth pulp, and chemical activity of acute inflammatory cells in the lesion underneath the tissue. Neutrophil lysosome enzymes enhance tissue damage and suppuration. The primary clinical difference between reversible and irreversible pulpitis is the pulp heat stimulation response. Reversible pulpitis's exaggerated yet insensitive cold response. Prolonged cold stimulation causes permanent pulpitis. Reversible pulpitis should respond to the removal of the causative stimuli. Healing and polypectomy are uncommon if the pulp is persistently irritated [4].

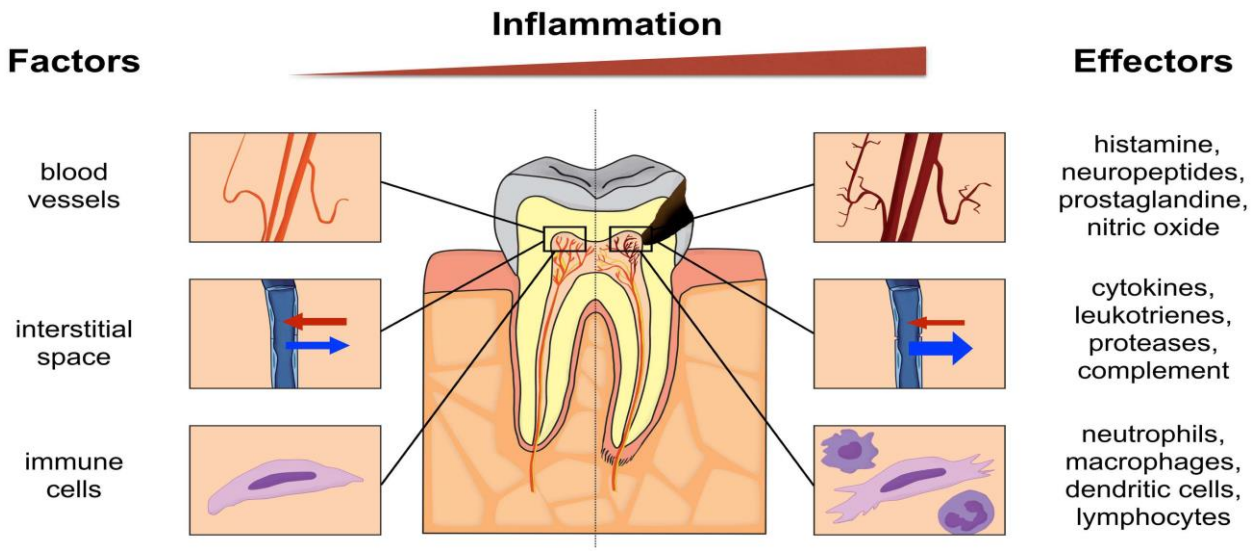

Figure 1.1: tooth with healthy pulp (left panel) and tooth with inflamed pulp (right panel)[4]

2.3. Causes and factors of inflammation:

Dentin pulp suffers various damage. Traumatic traumas, dental procedures, and restorative material can cause dentin-pulp alterations and pulp inflammation. Indeed, acids produced by bacterial metabolism following carious damage can solubilize and liberate fossilized dentin matrix proteins, such as growth factors. Dentin etching dissolves the layer smear plug and cosmetically demineralizes the dentin [5,6]. Dentin demineralization may release signaling chemicals from the matrix into pulp cells. After stimulating odontoblast secretion, reactive dentin forms [7,8]. Calcium hydroxide and mineral trioxide aggregates solubilize dentin [9,10]. Resinous monomers also reduce pulp cell development factors like FGF-2 and induce endoplasmic reticulum dentin sialoprotein and osteonectin accumulation [11]. These elements mineralize the extracellular matrix and need adequate assessment to work. Even with harmless resinous monomer concentrations, pulp cells experienced impaired mineralization due to buildup [12]. Odontoblasts can be destroyed by severe caries or deep cavity preparations. Odontoblasts in the Pulp chamber repair dentin. The physiological dentine secretes discontinuous tubular dentin. The intricate process of dentin reparative secretion involves the presence of various signals for receptive progenitor cells to differentiate and activate. TGF-β1, FGF-2, and BMP-2 and -4 are involved in the proliferation and differentiation of reparative dentin under carious lesions [5].

2.4. Inflammatory mediators in the pulp related to the injury conditions.

The dental pulp is designed to transmit various inflammation mediators that can combat inflammation factors that are distracting. Its mechanistic reaction starts with vascular changes that are regulated by 4/2 positive cells of toll-like receptors (TLR) and involves the release of detectable inflammatory cells Mediators [13].

Activation of T cells by the human dental pulp cells contributes to the reason are produced by microorganisms and their products [13]. The group includes odontoblasts, macrophages, dendritic cells, and endothelial cells. Some of these cells are capable of forming physiological barriers, identifying and transferring stimuli (e.g., odontoblasts), and differentiating (i.e., stem cells of the dental pulp)to restrict infection, signal damage, and encourage repair, respectively [14,15,16].

2.5 Odontoblast response to the various pulp injuries

The odontoblasts bordering the dental pulp behave as external stimulation sensors. These cells are cytoplasmic throughout the dentine and near to unmyelinated sensory Nerve fibers that spread in the inner half from the dental pulp to the dentine.

Intrinsic evidence supports an odontoblast position as sensory cells, which can detect external stimuli and transmit the signal to the neighboring neural cells, aided by the close application of the dentinal neural cells [15].

The data has been published. These cells have been shown to express transient receptor potential (TRP) ions. These channels are known for their direct ability to Due to thermal and chemical stimuli, mediate nociceptive functions.

Odontoblasts distribute vanilloid 1 transient receptor potential, which refers to Capability cation channel for noxious heat and transient receptors Melastatin 8 and ankyrin A1, which mediate cold sensations that are calm and noxious, respectively.

Furthermore, these receptors are responsive to chemical compounds. Stimulation while the pulp of dentin is the primary focus of Odontoblasts, which deposit a defense for bacteria/toxins and restorative materials. Reactive dentin, since they function as responsive sensor cells to dentin-solubilized signs of regeneration [17].

2.6 Diagnosis of pulp conditions

A correct diagnosis of the pulp condition in the Teeth affected by caries, dental procedures, or caries, in addition, other types of injury is essential to ensuring a proper result. Decision on treatment, with important specifics in this. If the pulp is vital or necrotic, reversibly or irreversibly inflamed, respect is essential. Patient diagnostic information is collected about Pain or discomfort background, trauma, or history of restorative treatments, clinical tests, outcomes Radiographic and clinical assessment of the teeth and the tissues around [18].

Rarely does the diagnosis take place on one observation, but rather on a variety of statements. The clinical situation can be so complicated that a correct decision on diagnosis and care needs a diagnostic approach consisting of several steps, a number of approaches for evaluating the condition Of Dental pulp.

To determine the status of pulp by the following clinical conditions and tests:

• Hypersensitivity response to the heat, cold reaction, electrical asymptomatic stimulation, or sensitivity to percussion. Teeth with significant caries.

• Pain involvement, existence, or duration; Combining pulp condition assessment tests.

• Testing or methods for electric or thermal pulp, Pulpal circulation assessment to assess if the pulp is vital or non-vital.

• Biological markers for Pulp inflammation, infection, or other tissue damage for the outcome prediction Of Treatment

2.7 How to collect biomarkers in pulp condition

These biomarkers have not only been clearly expressed in pulp tissue, but also in gingival fluid, which is accumulated within and outside the invasion. Dentine fluid to be examined without the whole pulp tissue being removed. Such details may be available and used in pulp diagnosis, measured accurately.

Inflammation by periodontal and pulpal does have similar characteristics: both display inflammation of soft tissue caused by Infection of bacteria. These pathological processes contribute to bone resorption at a later stage. (Bone damage, vertical or apical periodontitis). Therefore, both may be probable

The same biomarkers will reflect the pathos is. MMPs have been shown to be important biomarkers in this respect [19,20].

Direct way approaches, such as Intrapulpal conditions used Pulpal blood clinically less invasively; indirect approaches, such as dentine fluid collection or gingival crevicular fluid mediator assessment, may be achieved.

Dentin fluid is the extracellular fluid in the dentinal tubules It contains proinflammatory cytokines and infectious vasoactive compounds [21,22].

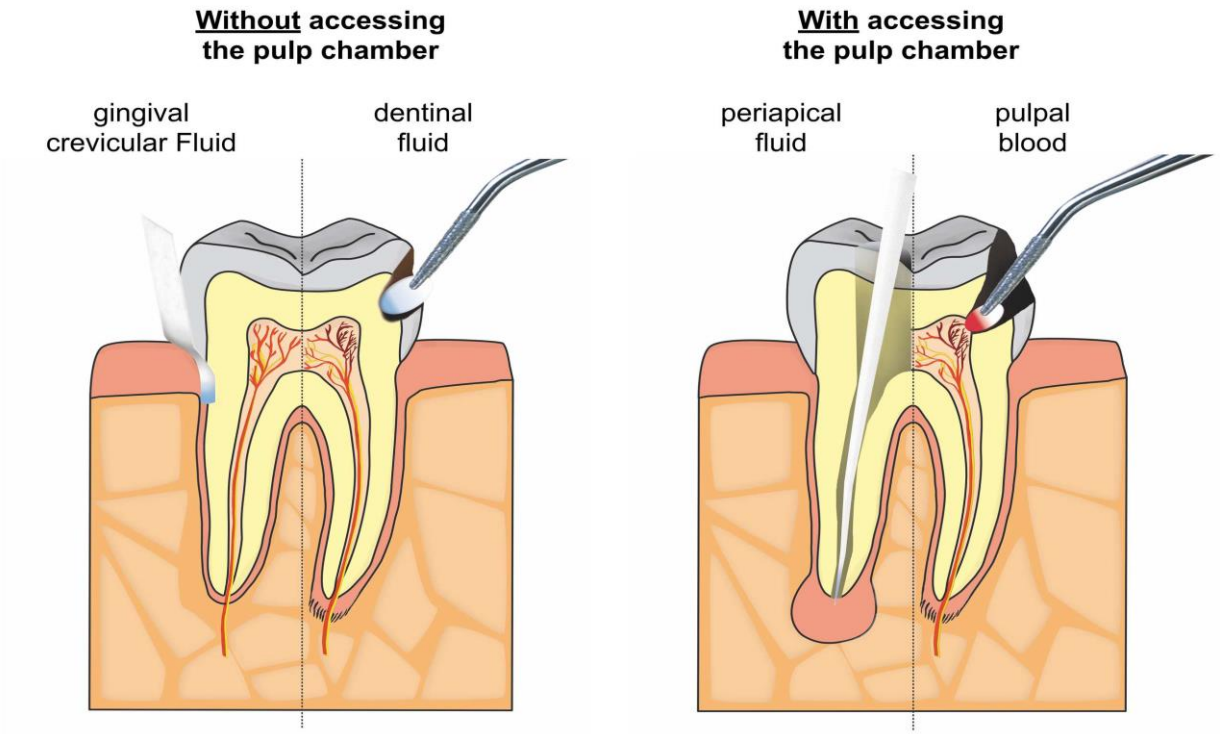

Figure 2: Actual and potential sampling sites to assay pulp mediators [4].

For pulpal diagnosis sampling from the gingival crevicular fluid, this perceived disadvantage can be resolved:(i)the production of natural features or healthy condition of periodontal; (ii)averaging a variety of positions on one or more teeth; (iii) a mixture of clinical and x-ray findings.

2.8 Biomarkers as inflammatory mediators in pulp condition and their action

Multiple pulpal cells, such as macrophages, generate IL-8, endothelial cells, lymphocytes, and fibroblasts. In vitro, the low IL-8 expression of odontoblast cells is important. It rises with a molecular pattern associated with pathogen Activation, lipopolysaccharide in particular.

This higher level is associated with increased PMNs in the pulp as IL-8 causes neutrophil chemotaxis and releases degraded enzymes during granulation. This is the result of the increase in the expression of IL-8.

In acute inflammatory responses, IL-8 is often defined as the primary regulator, and high levels can maintain and worsen acute inflammatory responses [23,24].

TNF-a is a pleiotropic molecule to increase the toxicity of leukocytes, stimulates and triggers inflammatory proteins in the acute stage, Generation of cytokine. TNF-a is a mediator against inflammation, critical for the response of dental pulp to disease [25].

Its macrophage synthesis is also enhanced via toll-like ligand receptors Binding in bacterial presence. Some inflammatory cytokines play a vital role in both growth and repair. Both functions vary based on concentration and situation [26,27].

Mesoporous matrix metalloproteases are important for the homeostasis of tissue and play a destructive role. Conditions and pulp inflammation, in particular, Alse MMPs, which change cell binding.

Their function is obvious but not very well understood in the breakdown of tissue. Dual inflammatory functions for MMP family proteins in

Innate and adaptive immune pathogenesis, defensive stimulation, and Tissue degradation [28].

By reducing the number of anti-inflammatory effects, MMP-3 generates Cells presenting macrophages and antigen, and substantially inhibiting the expression of IL-6 [29,30]. Like MMP-9 or gelatinase, PMNs, which are abundant in damaged tissue, are secreted mainly by healthy tissues. Since their primary purpose is to degrade MMP-9s, the extracellular ground material of collagen is typically considered a pulp tissue breakdown marker [30].

The role of MMPs in the pulp region is supported by the rise in MMP-9.

Levels of gingival crevicular fluid indicated Periodontal damage with severity according to its level, so MMP-9 may support as a connective tissue degradation marker.

There is proof of the relation between interleukin -8 and Mesoporous matrix metalloproteases -9. According to the findings of rapid MMP-9 induction of TNF-a and IL-8 Total human blood zymogen release,

Neutrophils associate with these three biomolecules; neutrophil stimulates IL-8

TNF-a is a potent activating neutrophil agonist for chemotaxis, and MMP-9 is mainly secreted via PMNs. Pulpitis is obviously powered by PMN Inflammation, typically with an invasion of neutrophils Adjoining pulp to dentin infected. Strong defense of neutrophils In Pulp infection; however, permanent damage to tissue may also be caused [31].

2.9 Criteria of ideal biomarkers

The biomarker must preferably be effective, safe to use, quick to monitor, affordable, and supportive of becoming a valid, non-invasive collection. It should, indeed, be highly sensitive to properly assess those with Infection (true positive) and precise to classify those without infection correctly (true negative) [32]. These parameters improve the biomarker's accuracy as a predictive and diagnostic tool and for better utilization.

Reflecting the reactions of the patients to medication. In addition, the quality of outcomes across various significant aspects of an ideal biomarker is influenced by racial classes, ages, and backgrounds [32].

2.10 Types of biomarkers in medicine

In medicine, a "biomarker" is a protein found in the blood that signals normal or pathological conditions. Pathogenic and pharmacological responses to therapy [33]. In general, a biomarker is any symptom that measures the severity of an ailment or a physiological state. Thus, biomarkers are vital to medicine. Studying and practicing illness mechanisms and courses provides insight. A substance called a biomarker is used to assess organ function or other health factors in an organism. Rubidium chloride, a radioactive isotope used to assess heart muscle perfusion, can also detect infection antibodies. Biomarkers, found in tissues or blood, detect changes in protein expression linked to disease development or therapy response. They can be specific cells, genes, gene products, enzymes, molecules, or hormones [34]. Because there are so many biomarkers used for different reasons, they have been grouped as follows: 1) biomarkers showing previously identified biomarkers;2) screening biomarkers, which are risk of illness incidences used to detect early-stage diseases; 3) diagnostic biomarkers, which show the presence of an illness; 4) staging biomarkers, which help determine disease stage and severity; and 5) prognostic biomarkers, which show disease severity and progression, including treatment response [35].

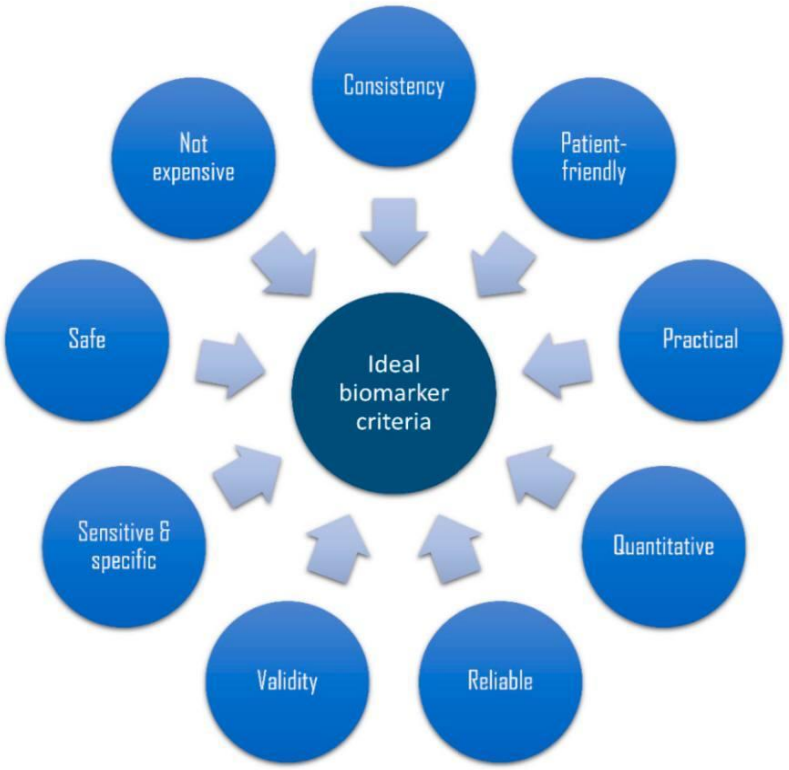

Figure 3. Criteria of ideal biomarkers [32].

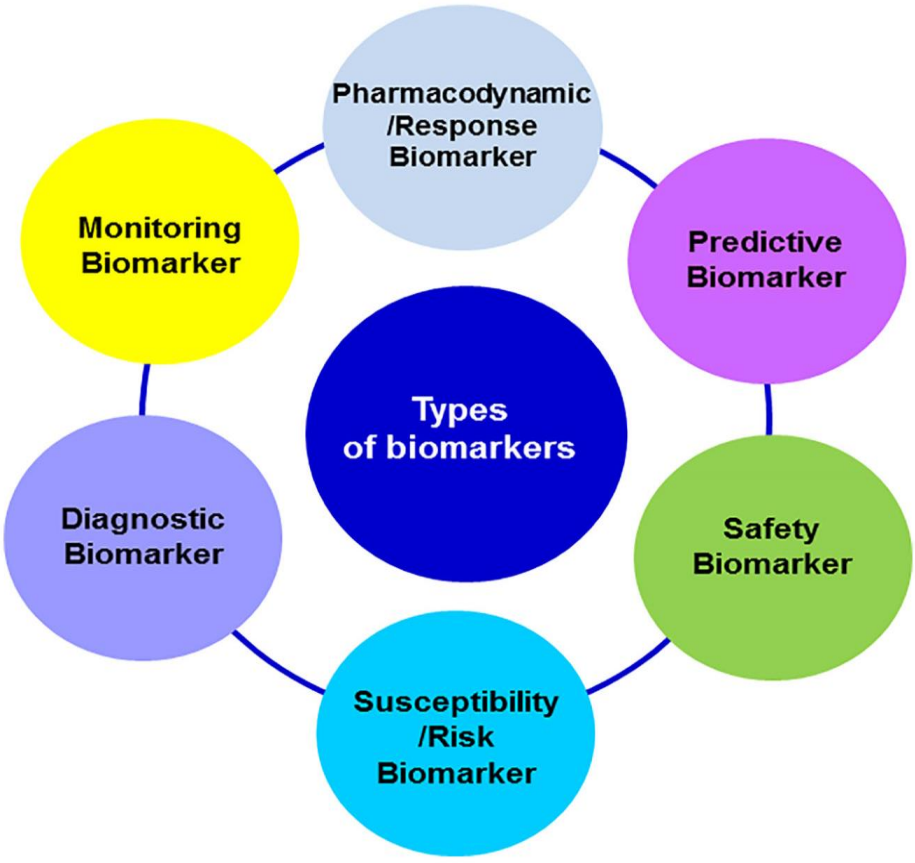

Figure 4: Types of biomarker [34].

2.11 Types of biomarkers in dentistry

2.11.1 Biomarkers in healthy Pulp:

Osteocalcin (OCN): Glycoprotein generating odontoblasts, OCN that is contained in the matrix of dentin, has been used as an Odontoblast/osteoblast-like mineralization marker, Differentiation in the stem cells of dental [36,37].

Thyrotropin-Releasing Hormone (TRH) Degrading Enzyme (DE): it extracellularly guides and functions to stop the cell regulated by peptides Signposting. In the dental pulp, TRH-DE was isolated by the study of microarrays and RT-PCR analysis in real time [38].

Metalloproteinase (MMP) matrix: synthesized MMPs are by connective tissue cells, such as fibroblasts, osteoblasts, Secreted into the extracellular matrix and odontoblasts. Several MMPs have been detected by polymerase chain reaction, Immunohistochemistry and PCR (reaction) [39].

Bone Morphogen Protein (BMP-2): The expression of Bone Morphogen Protein (BMP-2) during tooth cytodifferentiation, BMP2, occurs in postnatal conditions. From birth until about 20 days after birth, odontoblasts and ameloblasts [40].

Bone sialoprotein (BSP) is a crucial non-collagenous protein.

Protein is synthesized in mineralized connective tissue. There is really a fact allowed for cementum and dentin mineralization [41].

2.11.2 Biomarkers in healthy Periapical Tissue:

Matrix metalloproteinases (MMPs) are responsible for tissue degradation and remodeling. The periodontal system of the ligament is covered by MMPs Metalloproteinase Tissue Inhibitors [19].

Type I collagen pyridinoline cross-linked carboxyl - terminal telopeptide: Pyridinoline cross-linked carboxyl-terminal telopeptide of Type I collagen. Collagen in mineralized tissues represents the fundamental form of collagen type I. ICTP levels have risen. Numerous pathogens, such as T., are associated with them. P. gingivalis, intermedia, forsythensis, and T. denticola [42].

Osteocalcin: a non-collagenous protein mainly located in mineralized tissues, osteoblast-formed, and helps in the remodeling of bones. During gum disease, its level remains Unchanged, while in periodontal disease it increases [43].

Calprotectin: a protein containing calcium and zinc, has a protein that binds to the activity of antimicrobial agents and antifungals, and plays an important role in inflammation. Increased on-site production of Calprotectin defends epithelial cells from bacterial inflammation, especially P. gingivalis [44].

Osteonectin: a protein that is acidic and cysteine-containing, the initial mineralization process plays a critical role. Therefore, it is for periodontal disease detection; it may serve as a critical marker [44].

Osteopontin (OPN): is produced by osteoblasts as well as osteoclasts

About osteoclasts. Location of osteoclasts in the clear zone. Attachment, higher OPN concentration, which assists in Bones Remodeling. In periodontitis, OPN concentration rises [45].

Table 1: Biomarkers of Healthy Pulp and Periapical Tissue [46]

Biomarker	Role	Studies
Osteocalcin (OCN)	One of the reparative molecules and its production occurs in reaction to dental pulp injury and also helps in bone remodeling.	Pi et al[4] 2011 Elmeguid et al[5] 2013 Bernabei et al[10] 2014
Thyrotropin-Releasing Hormone (TRH)	Membrane-associated peptidase (ectopeptidase) and it cease s peptide-mediated cell signaling.	Yamamoto et al[6] 2012
Bone Morphogenic Protein (BMP-2)	Important in development of dental pulp , its absence results in reduced blood vessels and colligated pericytes.	Yang et al[7] 2012 Malik et al[22] 2018 Rakian et al[23] 2013
Bone sialoprotein (BSP)	Essential for mineralizing tissues, like bone, cartilage, dentin and cementum.	Boushell et al[8] 2011
Pyridinoline cross -linked carboxyterminal telopeptide of type I collagen	Type I collagen is the primary form of collagen present in mineralized tissues.	Mishra et al[9] 2014 Costalonga et al[24] 2014
Calprotectin	Antimicrobial and antifungal, critical role in inflammation	Silva et al[11] 2015
Osteopontin (OPN)	Helps in remodeling bones	Hans et al[12] 2012

2.11.3 Biomarkers in Caries:

Bone Sialoprotein (BSP): participates in the treatment of dentin Mineralization and modulation with MMP-2. BSP Production Productions It goes up by 8-fold during caries. BSP and MMP-2 are both Involved in the host protective mechanism that tends to the caries-affected areas of calcification [46].

Alkaline Phosphatase (ALP): Helps deposit alkaline phosphatase early. Tissue calcification and mineral compounds. Often called an odontoblast marker-like Distinction. ALP activity increases in pulp cells during repair and regeneration after damage [46].

Metalloproteinases (MMP) matrix: After decalcification, the host cell-derived MMPs refer to dentine by bacterial acids. Deterioration. MMP-1 (interstitial collagenase) and MMP-8, respectively (Derived from PMN-collagenase), in saliva can be quantified. MMP-20 is released, and its activation occurs during the progression of Caries [46].

2.11.4 Biomarkers in Reversible Pulpitis:

CXC chemokine ligand 10 (CXCL10): The community of chemokine ligands includes CXCL10. Chemokine family non-ELR CXC can affect many cells, including IFN-stimulated macrophages. Pulpititis selectively aggregates lymphocyte subsets. CXCL10-CXCR controls interactions in inflammatory dental pulp [47].

Human b-defensins (hBDs) Human b-defensins: The first line of defense against oral bacteria is them. They prefer electrostatic microbial surfaces. Hydrophobic interactions disrupt cell layers [47]

Prostaglandin E2: triggers the release of factors into osteoblasts That causes resorption of the osteoclast bone [48].

Interleukin 1 (IL-1beta) beta: is a protein and a member of IL-1beta.The Interleukin 1 family of cytokines. It is an integral mediator of the inflammatory reaction and inclusion in a variety of Cellular actions, including the proliferation of cells, differentiation, and apoptosis [26]

Osteocalcin: is a protein hormone that is noncollagenous and is found in Dentine and bone [36]

Inducible Synthase of Nitric Oxide (iNOS): is involved in the inflammatory cycle, releases significant amounts of NO over a long time, has a part in the non-specific immune system, and is hazardous in infections [24].

2.11.5 Biomarkers in Irreversible Pulpitis:

Gene-related peptide calcitonin (CGRP): occurs in two Forms in humans: alpha-CGRP and beta-CGRP. It is a potent vasodilator for peptides and can operate in transmission nociception [49].

Substance P: is a neuropeptide and a key mediator of Dental pulp inflammation [49].

Prostaglandin F2alpha: a natural material. PGF2alpha binds F2alpha to function as an in-prostaglandin receptor [48].

Interleukin-8 (IL-8): Promotes neutrophil migration into tissue, which degranulates and releases tissue-damaging enzymes [23].

Vascular endothelial growth factor (VEGF): A cell-generated protein increases blood vessel formation. This increases vascular growth and permeability [24].

Manganese superoxide dismutase (Mn-SODs): The host releases oxygen intermediates, molecules, during inflammation. These molecules also form incomplete oxygen. Decrease in mitochondrial matrix, in comparatively small proportions, Quantities in healthy cells. primarily found in the mitochondrial matrix [50].

Metalloproteinase-3 (MMP-3) matrix: Also known as Stromelysin-1 break some types of collagen, laminin, and elastin proteoglycans. It is involved in curing wounds and entering and controlling cellular nuclei, Transcription [29].

2.11.6 Biomarkers in Asymptomatic apical periodontitis:

Osteoprogerin (OPG) and RANKL: NF-KB ligand Activator of receptors (RANKL, also known as TRANCE, ODF, and OPGL is a recently identified member of the superfamily of Tumor necrosis factor, which encourages the survival of dendritic cells, induces hemopoietic osteoclastic differentiation, and precursors that lead to resorption of bones.16 The activity of RANKL is neutralized by binding to its TNF-receptor decoy superfamily Osteoprosteoprogerin (OPG) [51].

MMP-2 (Gelatinase): an important connective mediator in prolonged periodontal disease, tissue damage [39].

MMP-9: is a matrix that relates to the zinc-metalloproteinase family. Extracellular matrix involvement Deterioration [39].

2.11.7 Biomarkers Symptomatic apical periodontitis:

Tartrate-resistant acid phosphatase (TRAP or TRAPase): Enzyme metalloprotein acid phosphatase is tartrate-resistant. TRAP's functions include osteopontin/bone sialoprotein dephosphorylation, ROS production, iron transport, cell development, and differentiation.

2.11.8 Biomarkers in Chronic periodontitis:

MMP-8: degradation of collagen I, II, and III, respectively its primary feature

Large MMP-8 concentrations of gingival crevicular fluid have been identified to be associated with salivary fluid (SF) The incidence of periodontitis [52].

2.11.9 Biomarkers in Periapical Abscess:

Mesenchymal Stem Cells (MSCs): multipotent stromal cells Osteoblasts, myocytes, chondrocytes, and adipocytes can divide. The cell's body has a large, spherical nucleus with a prominent nucleolus, finely scattered nucleoli, and Chromatin components that shape the nucleus [46].

Oxidative stress index: Phagocytic penetration and bone resorption are host defense mechanisms against the invading pathogen. ROS generation is a significant disease pathogenic factor. The saliva's main antioxidant molecule is present [46].

2.11.10 Biomarkers in Periapical cysts:

Chemokines (RANTES, IP-10, and MCP-1): Small migration-related proteins (8-10kD). Activation of leukocytes and selectin causes inflammatory cell binding to vessel walls. Injury causes high CXCL12/SDF-1 chemokine levels in CD117+ mast cells and periapical inflammatory lesions [51].

Cytokines (IL-6): proteins released in response to Leukocyte-caused microbial agents and other damage-causing agents. Bone remodeling and activation involve IL-6. With immune cells, osteoclasts, and differentiation being the main source of periapical macrophages [53,54].

Table 2: Biomarkers of Diseases in Pulp and Periapical Tissue [46]

Disease	Sl.no.	Biomarker	Role	Studies
Caries	1.	Matrix Metalloproteinases (MMP)	Derived from host cells , participate in the destruction of dentin after bacterial acid demineralization	Tannure et al[25] 2012
	2.	Alkaline Phosphatase (ALP)	Repair and heal ing after pulpal injury	Hegde et al[26] 2014
Reversible Pulpitis	1.	Prostaglandin E_2	Multiple pro -inflammatory and immunomodulatory effects	Petrini et al[13] 2012
	2.	Interleukin 1 beta (IL-1beta)	Regulates immune and inflammatory reactions; stimulates bone resorption	Subaric et al[28] 2017
	3.	Osteocalcin	Regulation of bone mineralization	Elmeguid et al[5] 2013
Irreversible Pulpitis	1.	Substance P	Vasoactive mediator, immune mediator	Sattari et al[14] 2010
	2.	Matrix metalloproteinase-3 (MMP-3)	Hydrolysis of intercellular matrix	Teja et al[30] 2018
Asymptomatic Apical Periodontitis	1.	RANKL and Osteoprogerin (OPG)	Promotes dendritic cell survival, induces osteoclastic differentiation from hemopoietic precursors leading to bone resorption	Hanada et al[16] 2011
	2.	MMP-2 (Gelatinase)	Hydrolysis of intercellular matrix	Bhupinder et al[17] 2010
Chronic Periodontitis	1.	MMP-8	Degradation of collagen type I, II and III	Borujeni et al[14] 2015
Periapical Abscess	1.	Mesenchymal Stem Cells (MSCs)	Tissue repair and regeneration	Estrela et al[31] 2019
	2.	8-isoprostanes	Biological activity as inflammatory mediators that augments Pain perception	Raymond et al[19] 2011
Periapical Cysts	1.	Cytokines (IL-6)	Regulator of T - and B -cell growth, acute phase protein production	Araujo-Pires et al[20] 2014 Bracks et al[21] 2014

Problem statement

Diagnostic tools in dentral field for the examination of inflammatory pulpal and periapical condition still very primary and not effective in most casses specialy these in the early stage.

Conclusion

Healthy and diseased pulp and periapical tissue reflect physiologic and pathologic agents. Signs, symptoms, and test results can help diagnose the condition more accurately, and biomarkers are effective.

Conflict of interest: NIL

Funding: NIL

Reference

1. Zanini, M., Meyer, E., & Simon, S. 2017. Pulp inflammation diagnosis from clinical to inflammatory mediators: A systematic review. Journal of Endodontics, 43, 1033-1051.

2. Smith, A. J., Scheven, B. A., Takahashi, Y., et al. 2012. Dentine as a bioactive extracellular matrix. Archives of Oral Biology, 57, 109-121.

3. Glickman, G. N. 2009. AAE Consensus Conference on Diagnostic Terminology. Journal of Endodontics, 35, 1619-1620.

4. Rechenberg, D. K., Galicia, J. C., & Peters, O. A. 2016. Biological markers for pulpal inflammation: A systematic review. PLOS ONE, 11, e0167289.

5. Chmilewskx, F. Jeanneau, C., Laurent, P., & About, I. 2014. Pulp fibroblasts synthesize functional complement proteins involved in initiating dentin-pulp regeneration. The American Journal of Pathology, 184, 1991-2000.

6. Van Landuyt, K., Snauwaert, J., De Munck, J., et al. 2005. Systematic review of the chemical composition of contemporary dental adhesives. Biomaterials, 26, 1195-1211.

7. About, I., Bottero, M. J., de Denato, P., et al. 2000. Human dentin production in vitro. Experimental Cell Research, 258, 33-41.

8. Tziafas, D., Smith, A. J. & Lesot, H. 2000. Designing new treatment strategies in vital pulp therapy. Journal of Dentistry, 28, 77-92.

9. Graham, L., Cooper, P.R., Cassidy, N., et al. 2006. The effect of calcium hydroxide on solubilisation of bioactive dentine matrix components. Biomaterials, 27, 2865-2873.

10. Tomson, P. L, Grover, L. M., Lumley, P. J., et al. 2007. Dissolution of bioactive dentine matrix components by mineral trioxide aggregate. Journal of Dentistry, 35, 636-642.

11. Diamanti, E., Bletsa, A., Kitasako, Y., et al. 2013. Effect of resinous monomers on odontoblast-like cells. European Journal of Oral Sciences, 121, 222-228.

12. About, I., Camps, J., Mitsiadis, T. A., et al. 2002. Influence of resinous monomers on the differentiation in vitro of human pulp cells into odontoblasts. Journal of Biomedical Materials Research, 63, 418-423.

13. Staguet, M. J., Carrouel F., Keller, J. F., et al. 2011. Pattern-recognition receptors in pulp defense. Advances in Dental Research, 23, 296-301.

14. Jiang, H., Lolar, J., Wu, J.E., et al. 2006. Stem cells from human exfoliated deciduous teeth (SHED) differentiate into functional neurons. Journal of Dental Research, 85, 959-963

15. Maurin, J. C., Souble, M. L., Didier-Bazes, M., et al. 2004. Expression and localization of reelin in human odontoblasts. Matrix Biology, 23, 277-285.

16. Horst, O. V., Horst, J. A., Samudtala, R., & Dale, B. A. 2009. Caries induced cytokine network in the odontoblast layer of human teeth. BMC Immunology, 10, 5.

17. El Karim, I.A., Linden, G. J., Curtis, T. M., et al. 2011. Human odontoblasts express functional

thermo-sensitive TRP channels: implications for dentin sensitivity. Pain, 152, 2211-2223.

18. Levin, L. G., Law, A. S., Holland, G. R., et al. 2009. Identify and define all diagnostic terms for pulpal health and disease states. Journal of Endodontics, 35, 1645-1657.

19. Sorsa, T. Tiädethane L. & Sale, T. 2010. Matrix metalloproteinases (MMPs) in oral diseases. Oral Diseases, 10, 311-318.

20. Rechenberg, D. K. & Zender, M. 2014. Molecular diagnostics in endodontics. Endodontic Topics,30, 51-65.

21 .Zehnder, M., Rechenberg, D. K., & Thürlimann, T. 2019. Molecular diagnostics of pulpal and periapical inflammation. Journal of Endodontics, 45(6), 691-698.

22. Mente 1. Hutnagel 5., Leo, M., et al. 2016. Dentin fluid as a diagnostic medium for pulpitis. Clinical Oral Investigations, 20, 1595-1602.

23. Hahn, C. L. & Licehr, F. R. 2007. Innate immune responses of the dental pulp to caries, Journal of Endodontics, 33, 643-651.

24. Goldberg, M., Nieh, A. & Uzunoglu, E. 2015, Inflammatory and immunological aspects of dental pulp repair, Pharmacological Research, 99, 308-315.

25. Alabd, S., Yameny, A. The association between Tumor Necrosis Factor-alpha level (TNF-α) and moderate COVID-19 patients in Egypt. *Journal of Bioscience and Applied Research*, 2021; 7(4): 223-228. doi: 10.21608/jbaar.2021.251241

26. Pezel Bibatic Anic. Anic Brekalo, Brekalo I., et al. 2002. Detection of tumor necrosis factor alpha in normal and inflamed human dental pulps. Archives of Medical Research, 33, 482-484

27. Silva, A. C., Earia, M. R., Fontes, A., et al. 2009. Interleukin-1 beta and TF-alpha levels in the dental pulp of rat molars after tooth preparation. Brazilian Dental Journal, 20, 287-291.

28. Le, A. D., Zhang, X., Xie, Y., et al. 2007. Expression of matrix metalloproteinases in human dental pulp. Journal of Endodontics, 33, 108-112.

29. Eba, H., Murasawa, Y., LobaraK, et al. 2012. The anti-inflammatory effects of matrix metalloproteinase-3 on irreversible pulpitis. Journal of Endodontics, 38, 1206-1211.

30. Okamoto, T., Yoshioka, M., Nakano, T., et al. 2010. The expression of matrix metalloproteinase -9 and tissue inhibitor of metalloproteinase-1 in human dental pulp. Journal of Endodontics, 36, 1169-1173.

31. Victor, D. J., Subramanian, S., Katumaran, S. & Pradeep, A. R. 2014. Gingival stevicular fluid levels of matrix metalloproteinase-9 in patients with periodontitis. Journal of Indian Society of Periodontology, 18, 43-47.

32. Gul, S. S., Abdulkareem, A. A., Sha, A.M., & Rawlinson, A. 2020. Diagnostic Accuracy of Oral Fluids Biomarker Profile. Diagnostics, 10, 838.

33. Group, B. D. W., Atkinson Jr, A. J., Colburn, W. A., et al. 2001. Biomarkers and surrogate endpoints. Clinical Pharmacology & Therapeutics, 69, 89-95.

34. Majkic-Singh, N. 2011. Biomarkers in clinical medicine. Journal of Medical Biochemistry, 30, 1-4.

35. Manolio, T. A. 2003. Novel risk markers and clinical practice. New England Journal of Medicine, 349, 1347-1349.

36. Abd-Elmeguid, A., Abdeldayem, M., Kline, L. W., et al. 2013. Osteocalcin expression in pulp inflammation. Journal of Endodontics, 39, 865-872.

37. Pi, M., Wu, Y. & Quarles, L. D. 2011. GPRC6A mediates responses to osteocalcin in B-cells. Journal of Bone and Mineral Research, 26, 1680-1683.

38. Yamamoto, T., Murakami, M., Ishizaka, R., et al. 2012. Identification of thyrotropin-releasing hormone (TRH)-degrading enzyme as a biomarker. Dentistry, 2, 1000114.

39. Sekhon, B. S. 2010. Matrix metalloproteinases--an overview. Research and Reports in Biology, 1, 1-20

40. Yang, W., Harris, M., Cui, Y., et al. 2012. Bmp2 is required for odontoblast differentiation and pulp vasculogenesis, Journal of Dental Research, 91, 58-64

41. Boushell, L., Nagaoka, H. & Yamauchi, M. 2011. Increased matrix metalloproteinase-2 and bone sialoprotein response to human coronal caries. Caries Research, 45, 453-459.

42. Mishra, D., Sivaram Gopalakrishnan, K., Kumar, T.S.S., et al. 2015. Evaluation of salivary levels of ICTP in periodontal health and disease. Journal of Clinical and Diagnostic Research, 9, ZC50

43. Bernabei, R., Martone, A.M., Ortolani, E., et al. 2014. Screening, diagnosis, and treatment of osteoporosis. Clinical Cases in Mineral and Bone Metabolism, 11, 201.

44. Silva, N., Abusleme, L., Bravo, D., et al. 2015. Host response mechanisms in periodontal diseases. Journal of Applied Oral Science, 23, 329-355.

45. Hans, S. & Mali, A. M. 2012. Estimation of osteopontin levels in plasma in periodontitis. Journal of Indian Society of Periodontology, 16, 354.

46. Jain, A., Aurwade. V., Bahuguna, R. & Agarwal, A. 2020. Biomarkers of healthy and diseased pulp and periapical tissue: A review. University Journal of Dental Sciences, 6, 94-100.

47. Mejare 1., Axelsson, S., Davidson, T., et al. 2012. Diagnosis of the condition of the dental pulp: a systematic review. International Endodontic Journal, 45, 597-613.

48. Petria, M., Ferrante, M., Siavarelli L, et al. 2012. Prostaglandin E2 to diagnose between reversible and irreversible pulpitis. International Journal of Immunopathology and Pharmacology, 25, 157-163.

49. Sattari, M., Mozayeni, M. A., Matlook, A., et al. 2010. Substance P and CGRP expression in dental pulps with irreversible pulpitis. Australian Endodontic Journal, 36, 59-63

50. Oka, S., Hirai, J., Yasukawa, T., et al. 2015. A correlation of reactive oxygen species accumulation by depletion of superoxide dismutases, Biogerontology, 16, 485-501.

51. Araujo Pites, A. C., Erancisconi, C. F., Biguetti, C. C., et al. 2014. Simultaneous analysis of T helper subsets markers expression in periapical lesions. Journal of Applied Oral Science, 22, 336-346.

52. Boruieni, S. 1., Mayer, M. & Fickholz, P. 2015. Activated matrix metalloproteinase-8 in saliva as diagnostic test for periodontal disease. Medical Microbiology and Immunology, 204, 665-612.

53. Yameny, A. IL-6, TNF-α, IL-1β, and IFN-γ Cytokines as Core Inflammatory Biomarkers: Biological Roles, Diagnostic Utility, and Clinical Applications. *Journal of Bioscience and Applied Research*, 2025; 11(3): 1055-1061. doi: 10.21608/jbaar.2025.456942

54. Bracks, I. V., Armada, L., Goncalves, L. S. & Rites, F.R. 2014. Distribution of mast cells and macrophages and expression of interleukin-6 in periapical cysts. Journal of Endodontics, 40, 63-68.