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Research Article

Influence of systemic inflammatory biomarkers on periapical healing after root canal therapy

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ABSTRACT

Periapical healing following root canal therapy is a complex biological process influenced by microbial elimination, host immune response, and systemic health status. Growing evidence suggests that systemic inflammatory biomarkers may serve as valuable indicators of an individual's inflammatory burden and could influence the repair of periapical tissues after endodontic treatment. Biomarkers such as C-reactive protein, interleukins, tumor necrosis factor-alpha, erythrocyte sedimentation rate, and blood cell–derived inflammatory indices have been investigated for their potential role in predicting healing outcomes and identifying patients at increased risk of delayed tissue regeneration. Chronic systemic inflammatory conditions, including diabetes, cardiovascular disease, obesity, and autoimmune disorders, may further alter immune regulation and bone remodeling, thereby affecting treatment success. Advances in biomarker analysis, molecular diagnostics, and artificial intelligence have created new opportunities for personalized endodontic care through improved risk assessment and treatment monitoring. Understanding the relationship between systemic inflammation and periapical healing may enhance clinical decision-making, facilitate individualized treatment planning, and improve long-term prognosis. Continued research is necessary to establish standardized biomarker profiles and validate their routine application in endodontic practice.

Introduction

Root canal therapy is one of the most predictable and successful procedures in contemporary dentistry for eliminating infection from the root canal system and preserving natural teeth. The principal objective of treatment is to eradicate microbial pathogens, prevent reinfection, and facilitate the healing of inflamed or infected periapical tissues. Although advances in instrumentation, irrigation protocols, intracanal medicaments, and obturation techniques have significantly improved treatment outcomes, complete periapical healing is not achieved in every patient.

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Persistent inflammation, host immune variability, microbial persistence, and systemic health conditions may all influence the biological processes responsible for tissue repair and bone regeneration following endodontic treatment (Singh et al., 2025).

Periapical healing is a dynamic process involving coordinated interactions among immune cells, inflammatory mediators, vascular components, and bone-forming cells. Following successful elimination of intracanal infection, inflammatory activity gradually subsides, allowing regeneration of periodontal ligament fibers, deposition of new bone, and restoration of normal periapical architecture. However, excessive or prolonged inflammatory responses may delay healing by promoting osteoclastic bone resorption, impairing angiogenesis, and disrupting extracellular matrix remodeling. Consequently, increasing attention has been directed toward understanding host-related factors that influence these biological events beyond the local endodontic environment (Feher et al., 2021).

Systemic inflammatory biomarkers have emerged as promising indicators of the body's inflammatory status and may provide valuable insights into the healing potential following root canal therapy. Biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) reflect varying degrees of systemic inflammation and immune activation. Elevated levels of these biomarkers have been associated with chronic inflammatory disorders that may compromise tissue repair, alter bone metabolism, and prolong inflammatory responses, potentially affecting the prognosis of endodontic treatment.

The relationship between oral and systemic health has become an increasingly important focus of modern dental research. Oral diseases are no longer considered isolated conditions but are recognized as integral components of overall health. The broader concept of oral health emphasizes functional well-being, disease prevention, and the bidirectional interactions between oral and systemic conditions, reinforcing the need for comprehensive patient assessment before and after dental treatment (Lee et al., 2017). Similarly, individuals with systemic disorders characterized by chronic inflammation—including cardiovascular disease, diabetes mellitus, obesity, autoimmune diseases, and metabolic syndrome—often exhibit altered immune responses that may influence the repair of periapical lesions after root canal therapy.

The integration of dental and medical information has further highlighted the importance of systemic disease assessment in dental practice. Accurate documentation of medical conditions, particularly cardiovascular diseases and other chronic inflammatory disorders, allows clinicians to better understand patient-specific risks and tailor treatment strategies accordingly. Improved congruence between medical and dental records facilitates comprehensive patient management and may enhance prediction of treatment outcomes in endodontics (Patel et al., 2018).

Nutritional status and dietary habits also contribute substantially to systemic inflammatory regulation and oral microbial homeostasis. Emerging evidence indicates that nutrition influences the composition of the oral microbiome, immune function, and inflammatory mediator production, all of which can affect periodontal and periapical tissue healing. Diet-induced modulation of microbial diversity and inflammatory pathways may therefore represent an additional factor influencing healing following root canal therapy (Santonocito et al., 2025).

Although most investigations of periapical healing have focused on local treatment variables, growing

interest has shifted toward biologically active regenerative approaches and host-modulating therapies. The incorporation of platelet-rich fibrin (PRF), nano-hydroxyapatite, and other bioactive materials has demonstrated encouraging improvements in periapical tissue regeneration, emphasizing that successful healing depends not only on effective canal disinfection but also on optimization of the host healing response (Singh et al., 2025). Likewise, advances in restorative and biomaterial sciences continue to improve long-term clinical success through enhanced material performance and tissue compatibility, contributing indirectly to the preservation of treated teeth (Badr et al., 2024).

Recent investigations into pulp biology and tissue responses have further strengthened the understanding that host inflammatory regulation plays a central role in dental tissue repair. Studies evaluating pulpal responses to contemporary therapeutic agents demonstrate that inflammatory modulation and preservation of tissue vitality are essential components of successful regenerative outcomes, principles that are equally relevant to periapical healing after root canal therapy (Singh et al., 2026). Furthermore, research involving osteoconductive biomaterials has demonstrated the importance of favorable biological environments for bone regeneration, supporting the concept that both local and systemic factors collectively determine successful osseous healing (Feher et al., 2021).

Certain hereditary and systemic disorders also illustrate the close relationship between systemic physiology and oral health. Craniofacial developmental abnormalities and systemic syndromes frequently present with oral manifestations that influence dental treatment planning, healing capacity, and long-term prognosis, emphasizing the need for individualized patient assessment within endodontic care (Lauritano et al., 2019).

Given the increasing recognition of systemic inflammation as a determinant of tissue repair, evaluating inflammatory biomarkers offers an opportunity to improve prognostic assessment and personalize endodontic treatment strategies. Understanding the influence of systemic inflammatory biomarkers on periapical healing may facilitate earlier identification of patients at risk for delayed healing, improve treatment planning, support precision dentistry, and ultimately enhance the long-term success of root canal therapy. This review therefore examines the biological significance of systemic inflammatory biomarkers, their relationship with periapical tissue healing, current clinical evidence, and future perspectives for integrating biomarker-guided decision-making into endodontic practice.

2. Systemic Inflammatory Biomarkers and Their Biological Significance

Systemic inflammatory biomarkers are measurable biological molecules that reflect the intensity and progression of inflammatory responses occurring throughout the body. They play a critical role in regulating immune function, tissue repair, and bone remodeling, making them increasingly relevant to endodontic healing following root canal therapy. Periapical healing depends not only on the successful elimination of intracanal microorganisms but also on the host's ability to resolve inflammation and regenerate periapical tissues. Consequently, variations in systemic inflammatory status may significantly influence treatment outcomes by altering the balance between tissue destruction and repair (Lee et al., 2017; Singh et al., 2025).

The inflammatory response begins when tissue injury or microbial invasion activates innate immune cells such as neutrophils, macrophages, and dendritic cells. These cells release cytokines, chemokines, and acute-phase proteins that coordinate the recruitment of additional immune cells and stimulate tissue repair mechanisms. While acute inflammation is essential for eliminating pathogens and initiating healing, persistent systemic inflammation may promote prolonged cytokine release, osteoclast activation,

and delayed bone regeneration, thereby compromising periapical healing after endodontic treatment (Feher et al., 2021; Santonocito et al., 2025).

Advances in laboratory medicine have enabled the identification of numerous systemic inflammatory biomarkers that may serve as indicators of healing potential. These biomarkers can be measured through routine blood tests and provide valuable information regarding immune activation, inflammatory burden, and overall systemic health. Their integration into endodontic assessment has the potential to improve risk stratification and facilitate personalized treatment planning, particularly in patients with chronic inflammatory diseases (Patel et al., 2018; Singh et al., 2025).

2.1 Overview of the Systemic Inflammatory Response

Inflammation represents a highly coordinated biological response designed to protect tissues against infection and injury while promoting healing. The inflammatory cascade involves vascular changes, leukocyte migration, cytokine production, and activation of numerous signaling pathways that regulate tissue regeneration. During successful healing, pro-inflammatory mediators gradually decline and are replaced by anti-inflammatory cytokines and growth factors that stimulate collagen synthesis, angiogenesis, and bone formation (Feher et al., 2021).

Systemic inflammation differs from localized inflammation because circulating inflammatory mediators affect multiple organs and tissues simultaneously. Elevated systemic inflammatory activity may impair cellular differentiation, reduce osteoblastic function, increase osteoclastic bone resorption, and prolong inflammatory cell infiltration within periapical lesions. Consequently, individuals with persistent systemic inflammation frequently exhibit slower wound healing and greater susceptibility to chronic inflammatory diseases affecting the oral cavity (Lee et al., 2017; Santonocito et al., 2025).

The interaction between oral and systemic health has become an important component of modern dentistry. Oral inflammatory diseases can contribute to systemic inflammatory burden, while systemic disorders such as cardiovascular disease, diabetes mellitus, obesity, and autoimmune conditions may negatively influence oral healing responses. The integration of medical and dental information therefore becomes essential for comprehensive patient management and individualized treatment planning (Patel et al., 2018; Lee et al., 2017).

2.2 Major Systemic Inflammatory Biomarkers

Several circulating biomarkers have been investigated for their ability to reflect systemic inflammatory status and predict healing outcomes following endodontic therapy.

C-reactive protein (CRP) is one of the most widely studied acute-phase proteins synthesized by the liver in response to interleukin-6 stimulation. Elevated CRP concentrations indicate active systemic inflammation and have been associated with impaired wound healing, delayed bone regeneration, and chronic inflammatory disorders. Because CRP rapidly responds to inflammatory stimuli, it is considered a practical marker for evaluating systemic inflammatory burden before and after dental treatment (Patel et al., 2018).

Interleukin-6 (IL-6) functions as a multifunctional cytokine involved in immune regulation, acute-phase protein synthesis, and osteoclast differentiation. Increased IL-6 levels stimulate hepatic CRP production while promoting inflammatory cell recruitment and bone resorption. Persistent elevation of IL-6 may therefore delay periapical tissue repair and prolong inflammatory responses after root canal therapy (Feher et al., 2021).

Tumor necrosis factor-alpha (TNF-α) is another major pro-inflammatory cytokine produced primarily by activated macrophages. TNF-α

enhances leukocyte recruitment, stimulates matrix degradation, and activates osteoclast-mediated bone resorption. Excessive TNF-α activity has been implicated in chronic inflammatory diseases and may contribute to slower radiographic resolution of periapical lesions (Singh et al., 2025).

Interleukin-1 beta (IL-1β) plays an essential role in initiating inflammatory reactions by stimulating leukocyte activation, cytokine release, and osteoclast differentiation. Elevated IL-1β concentrations are associated with persistent inflammatory responses and increased bone destruction surrounding infected root apices. Monitoring IL-1β levels may therefore provide useful prognostic information regarding healing progression.

Erythrocyte sedimentation rate (ESR) represents a nonspecific laboratory marker of chronic inflammation. Although ESR lacks disease specificity, elevated values frequently indicate ongoing inflammatory activity and have been used alongside CRP to evaluate systemic inflammatory status in clinical medicine.

More recently, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as inexpensive inflammatory indices derived from complete blood counts. Increased NLR reflects enhanced innate immune activation and relative suppression of adaptive immunity, whereas elevated PLR may indicate persistent inflammatory stimulation.

Table 1. Major Systemic Inflammatory Biomarkers and Their Biological Significance in Periapical Healing

Biomarker	Primary Source	Biological Function	Potential Influence on Periapical Healing
C-reactive protein (CRP)	Liver	Acute-phase inflammatory protein	Indicates systemic inflammatory burden and may predict delayed healing
Interleukin-6 (IL-6)	Macrophages, T lymphocytes	Cytokine regulating acute inflammatory response	Promotes CRP synthesis, osteoclast activation, and inflammatory persistence
Tumor necrosis factor-alpha (TNF-α)	Activated macrophages	Pro-inflammatory cytokine	Increases bone resorption and prolongs tissue inflammation
Interleukin-1β (IL-1β)	Monocytes and macrophages	Mediates immune activation	Enhances osteoclast differentiation and inflammatory cell recruitment
Erythrocyte sedimentation rate (ESR)	Blood-based laboratory marker	Indicator of chronic inflammation	Reflects persistent systemic inflammatory activity
Neutrophil-to-lymphocyte ratio (NLR)	Peripheral blood cells	Marker of innate immune activation	Associated with increased inflammatory burden and delayed healing
Platelet-to-lymphocyte ratio (PLR)	Peripheral blood cells	Systemic inflammatory index	May indicate impaired tissue regeneration and chronic inflammation

2.3 Biological Significance of Systemic Biomarkers in Endodontic Healing

Systemic inflammatory biomarkers provide insight into the biological environment in which periapical healing occurs. Elevated inflammatory markers indicate a heightened immune response that may interfere with osteogenesis, collagen maturation, vascular regeneration, and resolution of inflammation. Conversely, lower inflammatory

activity generally favors successful tissue remodeling and radiographic healing after root canal therapy (Feher et al., 2021).

Bone regeneration within periapical tissues requires coordinated interactions among osteoblasts, osteoclasts, endothelial cells, fibroblasts, and immune cells. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α stimulate receptor activator of nuclear factor kappa-B ligand (RANKL), increasing osteoclast differentiation and accelerating bone resorption. Sustained cytokine activity therefore shifts the balance toward tissue destruction rather than regeneration, delaying complete healing of apical lesions (Singh et al., 2025).

Emerging evidence also suggests that nutrition, oral microbial composition, and systemic metabolic status influence inflammatory biomarker profiles. Dietary factors capable of modifying the oral microbiome may indirectly regulate systemic inflammation and immune homeostasis, thereby affecting healing capacity following endodontic treatment (Santonocito et al., 2025). Similarly, advances in regenerative endodontics have demonstrated that successful tissue repair depends upon controlling inflammation while promoting favorable biological environments for regeneration, highlighting the importance of inflammatory regulation in clinical outcomes (Singh et al., 2026).

The increasing emphasis on holistic oral healthcare recognizes that successful endodontic therapy cannot be evaluated solely by local factors. Comprehensive patient assessment should incorporate systemic inflammatory status, medical history, nutritional influences, and immune function to optimize treatment planning and improve long-term prognosis. Integration of medical and dental records may further enhance individualized care by facilitating identification of systemic conditions associated with impaired healing (Patel et al., 2018). Although studies such as Badr et al. (2024) primarily address restorative material performance, they reinforce the broader concept that long-term dental treatment success depends on careful consideration of biological as well as material-related factors. Collectively, these findings support the growing role of systemic inflammatory biomarkers as valuable adjuncts in precision endodontics and personalized oral healthcare (Lee et al., 2017; Singh et al., 2025).

3. Influence of Systemic Inflammation on Periapical Healing After Root Canal Therapy

3.1. Pathophysiology of Periapical Tissue Healing

Periapical healing following root canal therapy is a highly coordinated biological process that depends on the successful elimination of intracanal microorganisms, resolution of inflammation, and regeneration of damaged periapical tissues. Once root canal disinfection is achieved, inflammatory mediators gradually decline, allowing immune cells, fibroblasts, endothelial cells, osteoblasts, and mesenchymal stem cells to participate in tissue repair and bone regeneration. This process culminates in the restoration of normal periodontal ligament architecture and mineralized periapical bone.

The host immune response plays a pivotal role throughout each stage of healing. Initially, neutrophils and macrophages remove necrotic tissue and microbial remnants, while cytokines regulate the transition from inflammation to tissue regeneration. Balanced production of pro-inflammatory and anti-inflammatory mediators is essential because excessive or prolonged inflammatory activity may stimulate osteoclastogenesis, delay collagen deposition, and impair angiogenesis. Consequently, systemic inflammatory status can significantly influence local healing responses even after technically successful endodontic therapy.

Bone remodeling remains the cornerstone of periapical healing. Osteoblast-mediated bone formation must exceed osteoclast-mediated bone

resorption for radiographic healing to become evident. Experimental studies investigating regenerative biomaterials have demonstrated that appropriate scaffold properties and osteoconductive environments significantly enhance new bone formation, highlighting the importance of controlled inflammatory modulation during tissue repair (Feher et al., 2021). Similarly, improved regenerative outcomes observed with nano-hydroxyapatite and platelet-rich fibrin in endodontic retreatment emphasize the relationship between inflammation control and enhanced periapical regeneration (Singh et al., 2025).

3.2. Mechanisms Linking Systemic Inflammation with Delayed Periapical Healing

Systemic inflammation influences periapical healing through multiple interconnected biological pathways. Elevated circulating inflammatory mediators may amplify local inflammatory responses, prolong immune cell activation, and interfere with normal tissue regeneration. Chronic systemic inflammatory states frequently result in persistent production of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), which promote osteoclast differentiation and inhibit osteoblastic bone formation.

Persistent inflammatory cytokine activity also affects vascular integrity. Endothelial dysfunction reduces tissue perfusion and oxygen delivery, limiting the migration of reparative cells into healing periapical lesions. Furthermore, systemic inflammation increases oxidative stress, generating reactive oxygen species that damage extracellular matrix proteins and cellular DNA while impairing fibroblast proliferation and collagen synthesis.

Another important mechanism involves dysregulation of macrophage polarization. Successful healing requires the transition from pro-inflammatory M1 macrophages toward anti-inflammatory M2 phenotypes that promote angiogenesis, extracellular matrix deposition, and tissue remodeling. Chronic inflammatory diseases often impair this transition, thereby prolonging inflammatory destruction and delaying tissue repair.

Bone remodeling is similarly affected because inflammatory cytokines activate the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway, increasing osteoclast differentiation while suppressing osteoprotegerin activity. The resulting imbalance favors continued periapical bone destruction rather than regeneration, thereby prolonging radiographic healing after root canal treatment.

3.3. Influence of Systemic Diseases Associated with Chronic Inflammation

Several systemic disorders characterized by chronic low-grade inflammation have been associated with impaired wound healing and altered immune regulation. These conditions may reduce the predictability of periapical healing following root canal therapy.

Diabetes Mellitus

Diabetes mellitus represents one of the most extensively investigated systemic conditions affecting endodontic outcomes. Persistent hyperglycemia promotes advanced glycation end-product formation, oxidative stress, endothelial dysfunction, and excessive cytokine production. These alterations impair neutrophil function, delay angiogenesis, reduce collagen synthesis, and compromise bone remodeling. Consequently, diabetic patients frequently demonstrate slower healing of periapical lesions and an increased prevalence of persistent apical periodontitis.

Cardiovascular Disease

Patients with cardiovascular disease often exhibit elevated systemic inflammatory markers including C-reactive protein and IL-6. Shared inflammatory pathways between cardiovascular disease and

chronic oral infections suggest a bidirectional relationship. Accurate integration of medical and dental records has therefore become increasingly important for identifying cardiovascular comorbidities that may influence dental treatment planning and healing outcomes (Patel et al., 2018).

Obesity and Metabolic Syndrome

Adipose tissue functions as an active endocrine organ producing inflammatory cytokines including TNF-α and IL-6. Individuals with obesity and metabolic syndrome therefore exhibit persistent low-grade systemic inflammation that may impair immune regulation, vascular function, and bone metabolism. These alterations may delay periapical tissue regeneration despite adequate microbial control within the root canal system.

Autoimmune Disorders

Diseases such as rheumatoid arthritis and systemic lupus erythematosus are characterized by chronic immune activation and excessive cytokine production. Long-term immunosuppressive therapy may further modify healing responses, increasing susceptibility to persistent inflammation while simultaneously reducing regenerative capacity.

Chronic Kidney Disease

Chronic kidney disease is associated with accumulation of inflammatory mediators, oxidative stress, impaired mineral metabolism, and altered bone turnover. Collectively, these systemic changes may reduce osteoblastic activity and compromise periapical bone regeneration following endodontic treatment.

The modern concept of oral health emphasizes that oral tissues should be evaluated within the broader context of systemic health rather than as isolated anatomical structures, reinforcing the importance of considering systemic inflammatory status during endodontic treatment planning (Lee et al., 2017).

3.4. Interaction Between the Oral Microbiota and Systemic Inflammatory Burden

The oral microbiome plays a central role in the development and resolution of apical periodontitis. Persistent bacterial biofilms stimulate continuous release of lipopolysaccharides, microbial toxins, and pathogen-associated molecular patterns that activate innate immune pathways. While root canal therapy effectively reduces microbial load, systemic inflammatory status determines how efficiently the host resolves the remaining inflammatory response.

Individuals with chronic systemic inflammation often exhibit exaggerated cytokine responses to bacterial antigens. Consequently, even minimal residual bacterial stimulation may perpetuate inflammatory signaling and delay periapical healing. Conversely, successful elimination of intracanal microorganisms combined with balanced systemic immune regulation promotes rapid tissue repair and bone regeneration.

Complex interactions between oral microorganisms and systemic immune responses have further strengthened the concept that oral and systemic health are biologically interconnected. Oral manifestations associated with several systemic genetic disorders also illustrate the influence of systemic conditions on oral tissue development and healing (Lauritano et al., 2019).

Recent regenerative endodontic studies further support the concept that optimizing the local inflammatory environment through biologically active materials can significantly improve tissue repair. Enhanced periapical healing observed following the use of nano-hydroxyapatite combined with platelet-rich fibrin demonstrates the clinical importance of inflammation modulation in regenerative endodontics (Singh et al., 2025).

3.5. Nutritional Status, Oral Microbiome, and Inflammatory Biomarkers

Nutrition substantially influences systemic inflammatory status and immune competence. Diets rich in refined carbohydrates, saturated fats, and ultra-processed foods promote chronic low-grade inflammation, whereas Mediterranean-style dietary patterns rich in fruits, vegetables, whole grains, omega-3 fatty acids, and antioxidants reduce circulating inflammatory biomarkers.

Nutritional deficiencies involving vitamins C, D, A, and several trace minerals impair collagen synthesis, immune regulation, angiogenesis, and bone remodeling. Consequently, patients with poor nutritional status may experience slower periapical healing following endodontic treatment.

Diet also shapes the composition and diversity of the oral microbiome. Nutritional interventions capable of maintaining microbial homeostasis may indirectly reduce systemic inflammatory burden while supporting favorable healing conditions. Recent evidence has highlighted the close relationship between dietary habits, microbial diversity, and systemic inflammatory regulation, emphasizing nutrition as a potentially modifiable factor influencing oral and systemic health (Santonocito et al., 2025).

Emerging biological therapies are increasingly focused on preserving pulpal vitality and minimizing excessive inflammatory responses. Experimental investigations evaluating pulpal reactions after silver diamine fluoride application demonstrate the importance of understanding host inflammatory mechanisms when selecting minimally invasive therapeutic strategies (Singh et al., 2026). Although these findings primarily concern vital pulp therapy, they contribute to the broader understanding of inflammation-mediated tissue repair within endodontics.

Table 2. Influence of Systemic Inflammatory Conditions on Periapical Healing Following Root Canal Therapy

Systemic Condition/Factor	Primary Inflammatory Mechanism	Effect on Periapical Healing	Clinical Implication
Diabetes mellitus	Hyperglycemia, oxidative stress, elevated cytokines	Delayed bone regeneration and persistent inflammation	Closer follow-up and glycemic control
Cardiovascular disease	Elevated CRP and IL-6, endothelial dysfunction	Reduced vascular healing capacity	Comprehensive medical assessment before treatment
Obesity/Metabolic syndrome	Chronic low-grade inflammation, adipokine imbalance	Slower immune resolution and bone repair	Lifestyle modification may improve outcomes
Autoimmune disorders	Persistent immune activation	Prolonged inflammatory response	Individualized treatment planning

Chronic kidney disease	Altered mineral metabolism and chronic inflammation	Impaired bone remodeling	Multidisciplinary patient management
Poor nutrition	Deficiency of essential nutrients and antioxidants	Reduced collagen formation and delayed tissue repair	Nutritional counseling and optimization
Oral microbiome dysbiosis	Persistent bacterial stimulation	Sustained inflammatory signaling	Effective canal disinfection and maintenance
Regenerative biomaterial support	Enhanced osteoconduction and immune modulation	Improved periapical regeneration	Adjunctive regenerative strategies may enhance healing (Feher et al., 2021; Singh et al., 2025)

Overall, systemic inflammation influences virtually every phase of periapical healing, from immune regulation and angiogenesis to extracellular matrix remodeling and bone regeneration. Recognition of systemic inflammatory burden, combined with advances in regenerative endodontics and personalized patient assessment, may improve prediction of healing outcomes and facilitate more individualized treatment strategies (Lee et al., 2017; Patel et al., 2018; Singh et al., 2025). While Badr et al. (2024) primarily investigated biomaterial bonding in prosthetic dentistry rather than endodontic inflammation, their findings underscore the broader importance of biomaterial performance in achieving durable restorative outcomes that support long-term oral rehabilitation.

4. Clinical Applications, Evidence, and Future Perspectives

4.1. Evidence from Clinical and Translational Studies

Recent advances in endodontic research have highlighted the importance of systemic inflammatory biomarkers as adjunctive indicators for predicting periapical healing after root canal therapy. While conventional evaluation relies primarily on clinical findings and radiographic evidence, circulating biomarkers provide additional information regarding the host's inflammatory status and biological capacity for tissue repair. Biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been associated with inflammatory activity that may influence the resolution of apical periodontitis.

Several translational studies suggest that successful root canal therapy is accompanied by a gradual reduction in systemic inflammatory burden as local infection is eliminated. Patients exhibiting persistently elevated inflammatory biomarkers before or after treatment are more likely to demonstrate delayed osseous regeneration, prolonged inflammatory responses, or incomplete radiographic healing. These findings indicate that systemic inflammation may act not only as a consequence of chronic oral infection but also as an independent modifier of tissue repair.

The growing understanding of regenerative endodontics further supports the importance of host biology during healing. In a comparative investigation of endodontic retreatment, Singh et al. (2025) demonstrated that regenerative adjuncts such as platelet-rich fibrin (PRF) significantly enhanced periapical healing compared with conventional approaches, emphasizing that modulation of inflammatory and regenerative pathways can improve treatment outcomes. Although PRF primarily acts locally, its regenerative effects illustrate how biological

mediators interact with systemic inflammatory status to influence healing (Singh et al., 2025).

Similarly, experimental investigations into pulpal tissue responses have shown that successful tissue repair depends on controlled inflammatory regulation rather than complete suppression of inflammation. Singh et al. (2026) observed favorable pulpal healing following silver diamine fluoride application when inflammatory responses remained balanced, reinforcing the concept that regulated immune activity supports tissue regeneration. These findings may have implications for understanding inflammatory biomarker behavior during periapical repair following root canal treatment (Singh et al., 2026).

4.2. Integration of Systemic Biomarkers into Endodontic Diagnosis

The incorporation of systemic inflammatory biomarkers into routine endodontic assessment has the potential to improve diagnostic precision and individualized treatment planning. Traditional diagnosis focuses on pulp vitality testing, clinical examination, and cone-beam computed tomography (CBCT), yet these methods provide limited insight into the patient's systemic inflammatory environment.

Measurement of serum inflammatory biomarkers before treatment could identify patients who are predisposed to slower periapical healing due to chronic inflammatory disorders, metabolic disease, or immune dysregulation. Patients with elevated CRP, IL-6, or TNF-α concentrations may benefit from closer postoperative monitoring, longer recall intervals, and adjunctive regenerative procedures aimed at enhancing tissue repair.

Furthermore, integrating dental records with comprehensive medical information allows clinicians to recognize systemic diseases that may influence inflammatory biomarker profiles. Patel et al. (2018) demonstrated that improved congruence between electronic dental and medical records enhances identification of cardiovascular conditions and other systemic disorders, facilitating more comprehensive patient management. Such integrated healthcare systems may become increasingly valuable for biomarker-guided endodontic decision-making (Patel et al., 2018).

The broader concept of oral health also supports this integrated approach. Lee et al. (2017) emphasized that oral health should be viewed within the context of overall systemic health rather than as an isolated condition. Consequently, evaluation of systemic inflammatory biomarkers aligns with contemporary concepts of patient-centered and precision dentistry (Lee et al., 2017).

4.3. Emerging Diagnostic Technologies

Rapid advances in molecular diagnostics are expanding the clinical utility of inflammatory biomarkers. Point-of-care testing platforms capable of measuring CRP, cytokines, and inflammatory cell ratios from blood or saliva may soon provide chairside assessment of systemic inflammatory status before endodontic treatment.

Artificial intelligence (AI) and machine learning algorithms are also emerging as valuable tools for integrating biomarker profiles with radiographic findings, demographic variables, medical history, and treatment characteristics. These computational models may improve prediction of periapical healing by identifying complex relationships that cannot be recognized through conventional statistical analyses.

Salivary diagnostics represent another promising development because saliva contains numerous inflammatory mediators reflecting both local oral conditions and systemic health. Combined serum-saliva biomarker panels may improve diagnostic sensitivity while reducing patient discomfort associated with venipuncture.

Advances in regenerative biomaterials further complement biomarker-guided treatment. Osteoconductive scaffolds and collagen-based

regenerative membranes have demonstrated the capacity to support bone regeneration by creating favorable biological environments for tissue repair. Experimental evidence from Feher et al. (2021) demonstrated enhanced osteoconductive properties of collagen membranes, highlighting the importance of regenerative biomaterials in supporting inflammatory resolution and bone healing. Such technologies may ultimately be integrated with biomarker-based patient selection to optimize regenerative outcomes (Feher et al., 2021).

Table 3. Clinical Applications of Systemic Inflammatory Biomarkers in Endodontic Practice

Clinical Application	Relevant Biomarkers	Clinical Benefit	Potential Limitation
Preoperative risk assessment	CRP, IL-6, TNF-α	Identifies patients at higher risk for delayed healing	Biomarkers affected by systemic diseases
Prognostic prediction	CRP, NLR, PLR	Predicts likelihood of successful periapical repair	Lack of standardized cutoff values
Monitoring treatment response	CRP, ESR, IL-6	Evaluates reduction of systemic inflammation after therapy	Serial testing increases cost
Personalized treatment planning	Multiple biomarker panels	Supports individualized recall schedules and regenerative interventions	Limited availability in routine dental practice
AI-assisted predictive modeling	Combined biomarker datasets with imaging	Improves prediction accuracy using multidimensional data	Requires large validated clinical datasets
Integration with electronic health records	Medical history plus biomarker data	Enhances interdisciplinary management of medically compromised patients	Data integration challenges and privacy concerns
Regenerative endodontic decision-making	Inflammatory cytokines and growth factors	Guides use of biologically based regenerative therapies	Limited long-term clinical evidence

4.4. Current Limitations in Biomarker-Guided Endodontics

Despite promising developments, several barriers continue to limit the routine clinical use of systemic inflammatory biomarkers in endodontics. One major challenge is the absence of universally accepted reference values specific to periapical healing. Biomarker concentrations vary according to age, sex, medications, smoking status, obesity, stress, and numerous systemic diseases, making interpretation difficult.

Additionally, most published studies remain observational, involve relatively small patient populations, or evaluate only short-term healing outcomes. Considerable heterogeneity exists regarding biomarker selection, laboratory methods, timing of sample collection, and radiographic evaluation criteria, limiting direct comparison between investigations.

Another important limitation is that systemic inflammatory biomarkers are not disease-specific. Elevated CRP or cytokine concentrations may reflect unrelated infections, autoimmune disorders, cardiovascular disease, or metabolic dysfunction rather than endodontic pathology alone. Therefore, biomarker assessment should complement—not replace—clinical examination and radiographic interpretation.

Research involving restorative biomaterials further illustrates that treatment outcomes depend on multiple biological and material-related variables. Although Badr et al. (2024) primarily investigated bonding performance of CAD-CAM

restorative materials, their findings reinforce the broader principle that successful dental treatment relies on careful integration of biological and material sciences, an approach equally applicable to biomarker-guided endodontics (Badr et al., 2024).

4.5. Future Research Directions

Future investigations should focus on developing standardized biomarker panels capable of accurately predicting periapical healing across diverse patient populations. Large multicenter prospective studies are needed to establish clinically meaningful threshold values and validate biomarker-based prognostic models.

Multi-omics technologies including genomics, transcriptomics, proteomics, metabolomics, and microbiome analysis may provide a more comprehensive understanding of host inflammatory responses than single biomarker assessment. Integration of these molecular datasets with CBCT imaging and AI-driven predictive analytics could facilitate highly individualized treatment planning.

Dietary influences on systemic inflammation and oral microbial composition also warrant greater investigation. Nutritional status significantly affects immune regulation and microbial homeostasis, both of which contribute to tissue healing. Santonocito et al. (2025) emphasized the complex relationship between diet, oral microbiome composition, and systemic inflammatory responses, suggesting that nutritional interventions may become supportive strategies for improving endodontic healing outcomes (Santonocito et al., 2025).

Furthermore, expanding interdisciplinary collaboration among endodontists, physicians, immunologists, bioinformaticians, and regenerative medicine researchers will accelerate the development of precision endodontics. Broader recognition of oral-systemic health relationships, as emphasized by Lee et al. (2017), together with improved understanding of rare systemic conditions affecting oral tissues, as discussed by Lauritano et al. (2019), will further refine personalized treatment strategies (Lee et al., 2017; Lauritano et al., 2019).

Overall, the integration of systemic inflammatory biomarkers with advanced diagnostics, regenerative therapies, electronic health records, and artificial intelligence represents a promising future direction that may substantially improve prediction, monitoring, and enhancement of periapical healing following root canal therapy.

5. Discussion and Conclusion

5.1 Discussion

Periapical healing following root canal therapy is a multifactorial biological process that depends not only on effective microbial elimination and adequate canal sealing but also on the host's systemic inflammatory status. While conventional endodontic success has traditionally been evaluated through radiographic healing and symptom resolution, increasing attention has been directed toward the influence of systemic inflammatory biomarkers as potential predictors of healing outcomes. Elevated levels of biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and inflammatory blood cell indices may reflect an exaggerated systemic inflammatory response capable of delaying bone regeneration and prolonging periapical inflammation.

The interaction between systemic inflammation and local immune responses provides a biological explanation for the variability observed in healing after technically successful root canal therapy. Persistent systemic inflammation promotes continuous cytokine release, increased osteoclast activity, impaired angiogenesis, and dysregulated collagen remodeling, all of which may interfere with regeneration of periapical bone. Conversely, patients with well-controlled systemic health generally demonstrate more favorable healing

responses because inflammatory mediators return more rapidly to physiological levels, allowing tissue repair mechanisms to proceed efficiently (Lee et al., 2017).

Several systemic diseases associated with chronic inflammation further support this relationship. Diabetes mellitus, cardiovascular disease, obesity, autoimmune disorders, and chronic kidney disease have all been associated with altered immune regulation and delayed wound healing. These conditions frequently exhibit elevated circulating inflammatory biomarkers that may negatively influence the healing environment surrounding the root apex. The importance of accurately documenting systemic medical conditions within dental practice has therefore become increasingly relevant, as comprehensive medical records facilitate individualized treatment planning and improved prediction of clinical outcomes (Patel et al., 2018).

Bone regeneration remains one of the most critical determinants of successful periapical healing. Experimental evidence has demonstrated that tissue regeneration depends upon balanced inflammatory signaling, extracellular matrix remodeling, and osteoconductive support. Research investigating collagen membranes and regenerative biomaterials has highlighted the importance of creating biologically favorable environments that promote new bone formation and vascularization (Feher et al., 2021). Although these investigations were conducted in implant-related regenerative models, the biological principles governing bone repair are directly applicable to periapical lesion healing following endodontic treatment.

Recent advances in regenerative endodontics also reinforce the importance of controlling inflammation during healing. The improved periapical healing observed with regenerative adjuncts such as platelet-rich fibrin (PRF) combined with nano-hydroxyapatite suggests that modulation of inflammatory responses can significantly enhance tissue repair and bone regeneration after endodontic therapy (Singh et al., 2025). Similarly, investigations evaluating pulpal responses to novel therapeutic materials have demonstrated that favorable healing is closely associated with controlled inflammatory reactions and preservation of tissue vitality (Singh et al., 2026). These findings collectively support the concept that inflammatory regulation is central to successful endodontic outcomes.

Beyond systemic disease, nutritional status and oral microbial ecology may also influence inflammatory biomarker expression. Diet significantly affects the composition of the oral microbiome and the host immune response, potentially altering both systemic inflammation and local periapical healing. Anti-inflammatory dietary patterns may promote microbial homeostasis and reduce circulating inflammatory mediators, whereas poor nutritional habits may exacerbate chronic inflammation and impair tissue repair (Santonocito et al., 2025). This emerging relationship highlights the importance of considering lifestyle factors alongside conventional endodontic treatment planning.

The broader concept of oral health also supports a more integrated approach to endodontic care. Contemporary definitions recognize oral health as an essential component of overall systemic health rather than an isolated condition. Consequently, successful root canal therapy should be evaluated within the context of the patient's general health, immune competence, and inflammatory burden (Lee et al., 2017). Patients presenting with complex systemic conditions or genetic disorders that affect craniofacial development and immune regulation may require individualized treatment approaches because their healing responses may differ substantially from healthy individuals (Lauritano et al., 2019).

Technological advances may further enhance the clinical utility of systemic inflammatory biomarkers. Artificial intelligence, machine learning, and predictive analytics have the potential to integrate biomarker profiles with

radiographic findings, clinical history, and systemic health information to generate individualized prognostic models. Such approaches could improve patient stratification, optimize recall intervals, and facilitate precision endodontics. Although the present evidence is promising, standardized biomarker thresholds, longitudinal clinical studies, and multicenter validation remain necessary before routine clinical implementation can be recommended.

Finally, although restorative material performance primarily influences coronal seal integrity rather than systemic inflammation, durable restorative outcomes remain essential for preventing reinfection and preserving long-term treatment success. Advances in adhesive materials and restorative techniques continue to contribute indirectly to favorable endodontic prognosis by maintaining an effective coronal seal and protecting the treated tooth from microbial leakage (Badr et al., 2024).

5.2 Conclusion

Systemic inflammatory biomarkers represent an emerging and clinically relevant dimension in understanding periapical healing after root canal therapy. Growing evidence indicates that elevated systemic inflammatory activity may impair immune regulation, delay bone regeneration, and reduce the predictability of healing despite technically successful endodontic procedures. Integrating systemic health assessment with conventional clinical and radiographic evaluation may therefore improve prognostic accuracy and support personalized treatment planning.

Current research suggests that inflammatory biomarkers such as CRP, IL-6, TNF-α, ESR, NLR, and PLR possess considerable potential as adjunctive indicators of healing capacity. Their predictive value may be further enhanced through integration with regenerative therapies, advanced imaging, molecular diagnostics, and artificial intelligence-based predictive models. Regenerative strategies that actively modulate inflammation, including biologically active scaffold materials and platelet concentrates, further emphasize the importance of controlling the host inflammatory response to optimize clinical outcomes (Singh et al., 2025; Feher et al., 2021).

Nevertheless, routine clinical application remains limited by the absence of standardized biomarker thresholds, variability among patient populations, and insufficient long-term prospective evidence. Future multicenter studies should focus on validating biomarker panels, establishing evidence-based clinical guidelines, and integrating systemic inflammatory assessment into precision endodontic practice. Such developments have the potential to transform root canal therapy from a procedure focused primarily on microbial elimination into a comprehensive, patient-centered approach that incorporates systemic health, regenerative biology, and individualized risk prediction to maximize long-term periapical healing (Lee et al., 2017; Patel et al., 2018; Santonocito et al., 2025).

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