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Review

Regenerative Endodontic Procedures in Immature Necrotic Teeth Current Evidence and Future Directions

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Abstract

Immature permanent teeth with necrotic pulps present a complex challenge due to their underdeveloped root structures and fragile dentinal walls. Conventional treatments such as apexification have provided limited success in promoting continued root development and often leave teeth structurally compromised. Regenerative endodontic procedures (REPs) have emerged as a biologically based alternative, aiming to stimulate tissue repair and root maturation by leveraging the body's own healing mechanisms. The use of stem cells from the apical papilla, in combination with growth factors and suitable scaffolds, offers the potential for reestablishing functional pulp-like tissue. Clinical outcomes have included increased root wall thickness, apical closure, and resolution of periapical pathology, although the quality and consistency of regenerated tissue vary significantly between cases. The biological mechanisms that drive regeneration remain a key focus of research. Successful outcomes rely on the survival of stem cells, the signaling environment within the canal, and the compatibility of materials used during treatment. Irrigants, medicaments, and scaffold types directly affect the viability and differentiation of resident stem cells. Despite encouraging clinical observations, histological analyses frequently reveal tissue formation that differs from native pulp, raising questions about the regenerative process and long-term function. Innovation in this field includes the development of engineered scaffolds, bioactive molecules, gene therapy approaches, and extracellular vesicle-based treatments, all designed to enhance regeneration and overcome variability in patient responses. Emerging evidence suggests that a combination of biological precision and clinical standardization is critical for future success. Regenerative endodontics continues to evolve as a multidisciplinary field integrating biology, materials science, and clinical practice to improve outcomes for young patients with compromised teeth.

Keywords: *regenerative endodontics, immature teeth, stem cells, tissue engineering, pulp regeneration*

Introduction

Immature permanent teeth with necrotic pulps present a significant clinical challenge due to incomplete root development and thin dentinal walls, which compromise structural integrity and long-term prognosis. Traditional apexification methods, such as calcium hydroxide or mineral trioxide aggregate, have been widely used to induce apical closure but do not promote continued root maturation. These approaches can leave the tooth susceptible to fracture and long-term failure due to the lack of further root development. The limitations of conventional techniques have prompted the exploration of alternative biologically based therapies capable of regenerating the pulp-dentin complex and continuing root development in a more physiological manner (1).

Regenerative endodontic procedures (REPs) have emerged as a promising treatment strategy that leverages tissue engineering principles. These procedures aim to reestablish a functional pulp-like tissue in the canal space by creating an environment conducive to regeneration through the use of stem cells, scaffolds, and signaling molecules. The induction of bleeding into the root canal system is central to most REPs, providing a natural scaffold rich in growth factors and stem cells from the apical papilla. Clinical studies have reported favorable outcomes such as resolution of periapical pathology, increased root length, and thickening of root canal walls in immature teeth treated with REPs (2).

Despite these positive outcomes, variability in clinical protocols and patient responses highlight the need for deeper understanding of the biological mechanisms driving tissue regeneration in endodontics. The success of REPs is influenced by multiple factors including the degree of disinfection, scaffold quality, apical diameter, and host immune response. The presence and survival of stem cells in the apical papilla play a crucial role, and the preservation of these cells during treatment is essential for continued root development. Moreover, the role of microbial control, intracanal medicaments, and the type of irrigants used remain critical variables that can affect regenerative outcomes (3).

Future research in regenerative endodontics is exploring novel scaffolds such as platelet-rich plasma, bioengineered matrices, and synthetic peptides to enhance cell proliferation and differentiation. Additionally, the application of biologically active molecules such as bone morphogenetic proteins (BMPs) and transforming growth factor-beta (TGF-β) is being investigated to better mimic natural regenerative environments. While current regenerative protocols are largely based on clinical experience and case reports, ongoing clinical trials and basic science studies are expected to offer more robust evidence for standardized treatment approaches and improved patient outcomes (4).

Review

REPs have demonstrated considerable promise in managing immature necrotic teeth, yet several clinical and biological challenges remain. The variability in treatment outcomes across patients can often be attributed to differences in root canal disinfection, apical anatomy, and host response. While techniques such as the use of triple antibiotic paste and gentle irrigation aim to balance disinfection with stem cell viability, achieving a sterile yet biologically favorable environment remains complex (5). Moreover, inconsistencies in clinical protocols make it difficult to compare outcomes or standardize treatment guidelines across practices.

Recent advances have focused on improving scaffold quality and incorporating biologically active materials. The use of platelet concentrates, such as platelet-rich fibrin, has shown potential in enhancing the regenerative process by delivering concentrated growth factors directly into the canal space. These scaffolds not only support stem cell migration but may also influence differentiation and angiogenesis, which are essential for pulp tissue formation. Despite these innovations, long-term studies assessing the durability and functionality of the regenerated tissue are still limited, and further

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investigation is needed to validate these strategies in broader populations (6).

Clinical Outcomes and Challenges

REPs have become a preferred treatment approach for immature permanent teeth with necrotic pulps due to their potential to support continued root development and improve structural integrity. Over the past decade, clinical reports have documented outcomes such as resolution of apical periodontitis, thickening of root canal walls, and increased root length following REP treatments. However, these outcomes are not uniform across patient populations. Differences in case selection, disinfection methods, and operator experience contribute to a wide range of results, making reproducibility and predictability difficult to establish across clinical settings (7).

The ability of REPs to promote root maturation is closely tied to the presence and preservation of apical papilla stem cells. Cases with extensive infection or long-standing necrosis often exhibit limited regenerative responses due to compromised stem cell populations. Moreover, irrigation protocols that utilize high concentrations of sodium hypochlorite can negatively affect stem cell survival. Although alternative irrigants and lower concentrations have been proposed, consensus on the optimal disinfection regimen remains lacking. Calcium hydroxide, once avoided due to its potential to damage soft tissues, is now being reconsidered in diluted forms for its antimicrobial benefits and biocompatibility (8).

Radiographic evidence following REPs typically includes apical closure, periapical healing, and continued root elongation. Despite this, histological studies suggest that true pulp tissue regeneration is rare, and most cases result in the formation of tissue resembling periodontal ligament or cementum rather than functional pulp. This discrepancy between radiographic success and biological outcome has raised questions about the accuracy of current diagnostic tools in evaluating treatment success. Moreover, while pulp vitality testing can occasionally demonstrate positive responses, such findings are often inconsistent and cannot reliably confirm the presence of innervated pulp-like tissue (9).

Clinical protocols for REPs vary widely in terms of materials used, including intracanal medicaments, scaffold types, and the timing of each treatment phase. The triple antibiotic paste, commonly used for disinfection, can cause tooth discoloration due to minocycline content. Modifications using double antibiotic pastes or alternative agents such as calcium hydroxide seek to reduce this drawback, though potentially at the expense of antimicrobial efficacy. Blood clot formation, traditionally used as a natural scaffold, relies heavily on the patient's own bleeding response, which may be unpredictable or insufficient in some cases. Recent strategies incorporate platelet-rich fibrin and other bioactive materials to improve scaffold consistency, though their clinical advantages remain under investigation. The lack of standardized protocols across studies hinders meaningful comparisons and meta-analyses, leaving clinicians without a universally accepted framework to guide decision-making (10).

Biological Basis of Regeneration

Regenerative endodontic procedures depend on three foundational components of tissue engineering: stem cells, signaling molecules, and a supportive scaffold. The success of these procedures largely hinges on the preservation and activation of stem cells residing in the apical papilla, commonly referred to as SCAP. These cells exhibit high proliferative potential and are capable of differentiating into odontoblast-like cells when stimulated appropriately. Their presence in immature teeth offers a unique regenerative advantage, as they remain viable even in the presence of pulpal necrosis provided that the apical foramen remains open and the inflammatory environment is controlled (11).

Irrigation and disinfection protocols must be designed to minimize cytotoxicity to stem cells while effectively reducing bacterial load. Traditional endodontic irrigants such as sodium hypochlorite are effective antimicrobials but can be harmful to periapical tissues at higher concentrations. Research has indicated that

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concentrations below 1.5% can preserve SCAP viability without significantly compromising bacterial elimination. Likewise, chlorhexidine, while less cytotoxic, lacks the tissue dissolution capability of sodium hypochlorite and may interfere with cell adhesion. This balance between microbial control and stem cell preservation is delicate, and the long-term implications of sublethal chemical exposure on regenerative potential remain an area of active inquiry (12).

Scaffold formation within the canal plays a crucial role in supporting cellular migration and tissue organization. The induction of bleeding by over-instrumentation beyond the apex introduces a fibrin clot that contains platelets, inflammatory cells, and various growth factors. This natural matrix provides a three-dimensional structure that facilitates stem cell homing and angiogenesis. Vascular endothelial growth factor (VEGF), platelet-derived growth factor and TGF-β are among the key signals found in the clot that direct cell behavior during the healing phase. However, the concentration and bioavailability of these molecules can vary significantly between patients and even between treatment sessions in the same patient, leading to inconsistencies in regenerative outcomes (13).

The differentiation pathway of SCAP appears to be influenced by both mechanical and biochemical cues in the canal environment. In the presence of the right signaling molecules, SCAP can differentiate into odontoblast-like cells and lay down tubular dentin. However, many histological studies have found the formation of cementum-like, bone-like, or fibrous connective tissue instead of true pulp tissue. This suggests that the regenerative process often follows a reparative pathway rather than true tissue reconstitution. Additionally, the source of growth factors can alter the regenerative direction. External factors, such as the type of intracanal medicament or pre-existing inflammation, also appear to modulate stem cell fate decisions, further complicating predictability in clinical outcomes (14).

Future Directions and Innovations

Advances in biomaterials and biotechnology are rapidly influencing the trajectory of regenerative endodontics. Among the most promising areas is the shift from relying solely on patient-derived blood clots to engineered scaffolds with tailored biological activity. Synthetic and natural scaffolds are being designed to carry bioactive molecules, maintain structural integrity, and support cellular adhesion and proliferation. Materials such as hydrogels infused with growth factors or peptide sequences show potential to mimic the extracellular matrix and improve consistency in clinical results. These engineered matrices not only reduce reliance on patient-specific responses but also allow for better control over the microenvironment within the canal (15).

Bioactive molecules are being developed to guide stem cell behavior more precisely. Recombinant proteins like BMPs, fibroblast growth factors, and VEGFs have demonstrated the ability to influence differentiation pathways and promote angiogenesis in preclinical models. Delivery systems capable of releasing these factors in a controlled, sustained manner are being tested to extend their therapeutic effects while minimizing the risk of over-stimulation or undesirable tissue formation. Microencapsulation and nanoparticle-based carriers, for example, offer a way to release molecules in response to environmental triggers such as pH or enzymatic activity within the canal space (16).

The potential of gene therapy is being explored as well, with focus on modulating local cellular responses through transient or stable gene expression. Viral and non-viral vectors can be used to deliver DNA encoding for therapeutic proteins directly into the canal. This approach may offer a higher level of specificity in directing regeneration, potentially overcoming limitations of current scaffold-based systems. While safety and regulatory concerns remain, early-stage investigations have shown favorable results in modulating inflammation, enhancing vascularization, and promoting odontoblastic differentiation. Targeted gene delivery may also open possibilities for

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patients with compromised healing or systemic conditions that affect tissue regeneration (17).

Progress in cell-based therapies is also influencing new directions in regenerative endodontics. Allogeneic stem cells, derived from sources like dental pulp, bone marrow, or adipose tissue, are being tested as alternatives to relying solely on endogenous stem cells such as SCAP. These donor-derived cells may be expanded and primed before transplantation, increasing the likelihood of successful tissue formation. In addition, the concept of cell-free therapies has gained traction. Extracellular vesicles, particularly exosomes, carry proteins, mRNAs, and microRNAs that can influence recipient cell behavior. Their small size, stability, and immunomodulatory properties make them attractive candidates for therapeutic use in inflamed or infected endodontic environments (18).

Conclusion

Regenerative endodontics represents a transformative shift in managing immature necrotic teeth by integrating principles of tissue engineering and biologically driven healing. While current protocols have achieved encouraging clinical outcomes, inconsistencies highlight the need for deeper mechanistic insight and protocol refinement. Advances in biomaterials, cell therapy, and molecular signaling are paving the way toward more predictable and functional regeneration. Continued interdisciplinary research is essential to translate these innovations into reliable clinical solutions.

Disclosure

Conflict of interest

There is no conflict of interest.

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Ethical consideration

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Data availability

All data are available within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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