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Regenerative Endodontics: Biological Foundations, Clinical Protocols, and Emerging Innovations – A Narrative Review

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Abstract

The management of immature permanent teeth with necrotic pulps remains one of the most challenging scenarios in endodontics. Traditional apexification procedures, although effective in resolving infection, fail to promote continued root development and often result in structurally compromised teeth. Regenerative Endodontic Procedures (REPs) have emerged as a biologically based alternative that aims to restore the pulp–dentin complex and enable further root maturation. This narrative review discusses the biological basis of regenerative endodontics, emphasizing the tissue engineering triad of stem cells, scaffolds, and growth factors. It also evaluates current clinical protocols, disinfection strategies, and outcomes in comparison to apexification. Furthermore, the histological nature of tissues formed following REPs and future advancements in bioengineering, including 3D bioprinting and cell-based therapies, are explored. While true regeneration remains a challenge, REPs represent a paradigm shift toward biologically driven endodontic therapy with promising clinical outcomes.

Keywords: Regenerative endodontics; stem cells; scaffolds; pulp regeneration; apexification; tissue engineering

Introduction

The treatment of immature permanent teeth with necrotic pulps has historically relied on apexification using calcium hydroxide or mineral trioxide aggregate (MTA). While these techniques successfully induce apical barrier formation and resolve periapical pathology, they do not facilitate continued root development, leaving the tooth with thin dentinal walls and increased susceptibility to fracture [1,2]. Long-term use of calcium hydroxide has also been associated with structural weakening of dentin [2].

Regenerative endodontics has revolutionized this paradigm by introducing biologically based procedures aimed at restoring the vitality of the pulp–dentin complex. These procedures promote continued root maturation, increased dentinal thickness, and improved fracture resistance [3,4]. According to the American Association of Endodontists (AAE), regenerative endodontics encompasses biologically based procedures designed to replace damaged dental tissues and restore normal physiologic function [5].

The clinical objectives of regenerative endodontics are hierarchical:

1. Primary goal: Elimination of symptoms and healing of periapical tissues
2. Secondary goal: Continued root development (lengthening and thickening)
3. Tertiary goal: Restoration of pulp vitality and sensory function [5]

Biological Foundations:

Tissue Engineering Triad

The success of regenerative endodontics depends on the integration of three fundamental components: stem cells, scaffolds, and growth factors [4]. Recent advances have emphasized that biomaterial-driven modulation of stem cell behavior plays a crucial role in improving regenerative outcomes [6,7].

1. Stem Cells

Stem cells play a pivotal role in regeneration due to their ability to proliferate, differentiate, and form new tissue. Among dental stem cells, Stem Cells from the Apical Papilla (SCAP) are considered crucial due to their high proliferative capacity and dentinogenic potential [8].

Recent experimental models have demonstrated that stem/progenitor cell-mediated regeneration can lead to de novo pulp formation with dentin deposition, closely mimicking natural pulp–dentin architecture [9]. This highlights the potential of cell-based regenerative therapies beyond current clinical approaches.

2. Scaffolds

Scaffolds provide a three-dimensional framework that supports cell migration and proliferation. Traditionally, blood clot formation acts as a natural scaffold [10].

However, recent systematic evidence suggests that advanced scaffolds significantly improve regenerative outcomes, particularly in terms of root maturation and apical closure [11]. Platelet concentrates such as PRP and PRF further enhance angiogenesis and tissue regeneration [12,13].

Additionally, material-based scaffold strategies, including bioactive polymers and hydrogels, are now being explored to provide controlled release of growth factors and improved cellular organization [14].

3. Growth Factors

Growth factors embedded in dentin matrix regulate cellular differentiation and tissue formation [8].

Recent studies emphasize that bioengineered scaffolds can modulate growth factor delivery, improving cellular signaling and regenerative efficiency [15,16]. This integration of materials science with biology represents a major advancement in regenerative endodontics.

Clinical Protocols

Successful regenerative endodontics requires effective disinfection of the root canal system while preserving stem cell viability and growth factor activity [17].

Irrigation

Sodium hypochlorite (NaOCl) is widely used due to its antimicrobial properties; however, high concentrations are cytotoxic to stem cells. Therefore, lower concentrations (approximately 1.5%) are recommended to balance disinfection and biocompatibility [17,18].

Dentin Conditioning

Ethylenediaminetetraacetic acid (EDTA, 17%) plays a crucial role in removing the smear layer and releasing dentin-derived growth factors, thereby enhancing stem cell attachment and differentiation [19].

Intracanal Medicaments

Calcium hydroxide is preferred due to its favorable effect on stem cell survival [6]. Alternatively, triple antibiotic paste (TAP) can be used, but its concentration must be carefully controlled to avoid cytotoxic effects [18].

Coronal Seal

A tight coronal seal is essential to prevent reinfection. Materials such as MTA and Biodentine are commonly used due to their bioactivity and sealing ability [1].

Comparative Effectiveness:

REPs vs Apexification [TABLE 1]

Both apexification and regenerative procedures demonstrate high success rates in resolving periapical pathology. However, regenerative endodontics provides superior structural outcomes.

Studies have shown that regenerative procedures result in:

1. Significant increase in root width
2. Continued root lengthening
3. Apical closure with strengthened dentinal walls [20]

In contrast, apexification does not promote further root development and leaves the tooth structurally

Volume 9, Issue 3; May-June 2026; Page No 95-99

compromised [2]. Additionally, regenerative procedures show a higher probability of returning pulp vitality compared to apexification [21].

While regenerative procedures already demonstrate superior structural outcomes compared to apexification [20], recent analyses indicate that the type of scaffold used plays a critical role in clinical success, influencing root length, dentinal wall thickness, and apical closure [7].

This reinforces the concept that regenerative endodontics is not just a procedure but a biologically modulated therapeutic system.

Histological Outcomes

Regeneration vs Repair

Despite promising clinical and radiographic outcomes, true regeneration of the pulp–dentin complex remains limited. Histological studies reveal that the tissue formed within the canal space is often a combination of cementum-like, bone-like, and periodontal ligament-like tissues rather than true pulp tissue [22]. emerging experimental evidence demonstrates that controlled stem cell delivery and scaffold design can achieve pulp-like tissue with organized dentin formation [23].

Although this reparative tissue does not fully replicate the original pulp structure, it contributes to root maturation, apical closure, and increased fracture resistance, thereby providing significant clinical benefits [24].

Future Perspectives In Regenerative Endodontics

1. 3D Bioprinting and Biomaterials

Advances in 3D bioprinting allow precise placement of cells, scaffolds, and signaling molecules, enabling the development of customized tissue constructs for dental regeneration [11,23].

Modern regenerative models demonstrate that engineered constructs can replicate pulp-like tissue organization, bringing clinical applications closer to reality [6].

2. Cell-Based Therapies

While current REPs rely on cell homing, future approaches involve stem cell transplantation and ex vivo expansion, allowing controlled delivery of specific cell populations [6].

Experimental models confirm that stem/progenitor cell transplantation can achieve true pulp regeneration with dentin formation, representing a significant step toward complete biological restoration [24].

3. Advanced Scaffolds

Innovative biomaterials such as hydrogels and bioengineered matrices are being developed to enhance cell viability, vascularization, and tissue organization [11].

Recent research highlights the importance of material-based strategies in enhancing pulp regeneration, including bioactive scaffolds capable of directing stem cell differentiation and tissue organization [15].

Hydrogels, nanofibrous scaffolds, and injectable biomaterials are being developed to mimic the extracellular matrix and support vascularization.

4. Experimental Models and Translational Research

Recent literature emphasizes the importance of standardized in vitro and in vivo models for studying pulp regeneration [6]. These models are critical for bridging the gap between laboratory research and clinical application.

5. Current Trends and Clinical Translation

Recent reviews highlight that regenerative endodontics is rapidly evolving, with increasing integration of biomaterials, stem cell biology, and clinical protocols [9].

Despite challenges, the field is moving toward predictable, biologically driven regeneration rather than repair, marking a paradigm shift in endodontic therapy [16].

Conclusion

Regenerative endodontics represents a significant advancement in the management of immature necrotic teeth by shifting the focus from artificial barriers to biologically driven tissue regeneration. The integration of stem cells, scaffolds, and growth factors has resulted in improved clinical outcomes, including continued root development and enhanced structural integrity.

Although true pulp regeneration remains an ongoing challenge, current regenerative procedures provide predictable clinical success and improved prognosis compared to conventional apexification. With

Volume 9, Issue 3; May-June 2026; Page No 95-99

advancements in tissue engineering, stem cell therapy, and biomaterials, the future of regenerative endodontics holds the potential for complete restoration of the pulp–dentin complex.

Tables Table 1

Parameter	REPs	Apexification
Root length	↑	No change
Root thickness	↑	No change
Vitality	Possible	No
Fracture risk	↓	↑

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Volume 9, Issue 3; May-June 2026; Page No 95-99

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Volume 9, Issue 3; May-June 2026; Page No 95-99