

NARRATIVE REVIEW

Regenerative endodontics: Reimagining the healing potential of the dental pulp- A narrative review.

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Abstract

Regenerative endodontics represents a transformative shift in dental therapeutics, focusing on restoration of the dentin–pulp complex through biologically driven processes rather than conventional replacement strategies. This review integrates principles of stem cell biology, tissue engineering, and molecular signalling, and highlights recent advances including exosome-based therapies, advanced scaffold technologies, and gene therapy approaches. Clinical outcomes, challenges, and future directions are also discussed to provide a comprehensive overview for contemporary endodontic practice.

KEYWORDS

regenerative endodontics, stem cells, scaffolds, exosomes, pulp regeneration, tissue engineering

1 | INTRODUCTION

Regenerative endodontics has emerged as a true paradigm shift in modern dental practice, moving away from conventional approaches that focus on removing and replacing damaged tissues toward biologically driven strategies aimed at restoring the dentin–pulp complex. At its core, this field is built upon the principles of tissue engineering, integrating stem cells, scaffolds and signalling molecules to promote natural healing and regeneration. Dental stem cells, particularly those derived

from the apical papilla and pulp, have shown remarkable potential in re-establishing tissue vitality. Recent innovations such as exosome-based therapies, biomimetic and nanostructured scaffolds, and targeted gene modulation have further strengthened the regenerative potential, offering more precise control over cellular responses. Additionally, the incorporation of growth factors along with angiogenic and neurogenic signals along with 3D bioprinting, are opening new avenues for achieving functional and structural regeneration in a more predictable manner.² Despite these encouraging developments, regenerative endodontics still faces several clinical and translational challenges. Variability in

treatment protocols, concerns regarding long-term predictability, potential immune responses and regulatory limitations continue to influence its widespread adoption in routine practice. While clinical success has been well documented, particularly in immature teeth, extending these outcomes to mature teeth remains an area of ongoing research. Nevertheless, the rapid progress in biological understanding and technological innovation underscores the immense potential of this field. This review aims to present a comprehensive and clinically relevant overview by integrating current evidence, highlighting recent advancements and critically addressing existing challenges, thereby guiding future directions in regenerative endodontic therapy.

2 | BACKGROUND

The foundation of regenerative endodontics lies in the principles of tissue engineering, commonly described as the triad of: cells, signalling molecules and scaffolds. Stem cells, derived from the apical papilla and dental pulp, play a central role due to their ability to proliferate and differentiate into odontoblast-like cells. These cells can be recruited into the disinfected canal space through a process known as cell homing, which eliminates the need for exogenous stem cell transplantation. Signalling molecules, including growth factors released from dentin matrix and platelet concentrates, regulate cellular activities such as migration, proliferation, and differentiation. Platelet-rich fibrin (PRF) has gained considerable attention due to its autologous nature and sustained release of bioactive factors, promoting angiogenesis and tissue maturation within the root canal system. Scaffolds serve as a three-dimensional framework that supports cell attachment and tissue organization. While the traditional blood clot acts as a natural scaffold, modern advancements have introduced synthetic and natural biomaterials such as hydrogels and bioengineered matrices. These scaffolds not only provide structural support but also facilitate controlled delivery of growth factors and enhance vascularization. Clinical protocols in regenerative endodontics emphasize a balance between effective disinfection and preservation of stem cell viability. The use of low-concentration irrigants and minimal instrumentation helps maintain the integrity of dentinal structures and stem cell niches. Induction of bleeding into the canal space or placement of biomaterials allows the formation of a conducive environment for tissue regeneration, followed by a hermetic coronal seal to prevent reinfection.

3 | MATERIALS AND METHODS

We used PubMed, MEDLINE Ovid, and Cochrane Database to perform this review. The following keywords were used to search recent literature: 1- Regenerative endodontics. 2- Pulp regeneration dentistry. 3- Stem cells endodontics. 4- Scaffolds tissue engineering dental pulp. 5- Cell homing endodontics. 6- Exosomes regenerative dentistry. 7-

Biomaterials regenerative endodontics. Biological principles and clinical protocols related to regenerative procedures, including disinfection strategies, scaffold placement, stem cell recruitment, and coronal sealing techniques are compared in this review. Regenerative endodontic procedures are primarily aimed at restoring the vitality of the pulp-dentin complex through biologically driven mechanisms. Unlike conventional endodontic therapy, regenerative procedures emphasize healing and functional restoration rather than replacement, making them a central therapeutic strategy in modern endodontics.

4 | THE BIOLOGICAL TRIAD: CELLS, SIGNALS, AND SCAFFOLDS

Biological Basis of Regenerative Endodontics. The biological foundation of regenerative endodontics is deeply rooted in the principles of tissue engineering, classically defined by the triad of cells, signalling molecules, and scaffolds. These components interact in a highly coordinated manner to recreate a functional dentin-pulp complex rather than merely repairing damaged tissue. This integrated approach reflects a paradigm shift toward biologically driven healing, where the emphasis is on restoring vitality, function, and structural integrity of the tooth. According to Murray PE et al., regenerative endodontics represents a transition from conventional replacement therapies to biologically based procedures aimed at true tissue regeneration rather than repair.²⁴ Among these components, stem cells—particularly stem cells from the apical papilla (SCAP) and dental pulp stem cells (DPSCs)—play a pivotal role. These cells exhibit high proliferative potential and the ability to differentiate into odontoblast-like cells capable of forming dentin. As described by Sonoyama W et al., SCAP are especially important due to their survival in infected environments and their critical role in continued root development. Modern regenerative strategies emphasize cell homing, a concept highlighted by Lovelace TW et al., which involves recruitment of the patient's own stem cells into the disinfected canal space via chemotactic signalling, thereby eliminating the need for exogenous cell transplantation. The success of this process largely depends on preservation of apical tissues and maintenance of a favourable microenvironment.²¹ Signalling molecules are equally essential, as they regulate cellular behaviour through complex biochemical pathways. Growth factors such as transforming growth factor-beta (TGF- β), bone morphogenetic proteins (BMPs), and vascular endothelial growth factor (VEGF), released from the dentin matrix during treatment, play a crucial role in guiding stem cell migration, proliferation, differentiation, and angiogenesis. Galler KM et al. emphasized the importance of dentin-derived growth factors in orchestrating regenerative responses. In addition, platelet concentrates, particularly platelet-rich fibrin (PRF), have gained attention due to their autologous nature and sustained release of bioactive molecules. According to Choukroun J, PRF enhances vascularization and tissue maturation, thereby improving the predictability of regenerative outcomes. Scaffolds provide the structural framework necessary for tissue organization by acting as a

three-dimensional matrix that supports cell attachment and proliferation. Traditionally, the blood clot has been used as a natural scaffold due to its simplicity and biological compatibility. However, advancements in biomaterials have led to the development of engineered scaffolds such as hydrogels, collagen matrices, and synthetic polymers. Huang GTJ et al. highlighted that such biomimetic scaffolds not only improve mechanical stability but also facilitate controlled release of growth factors and enhance angiogenesis, thereby optimizing the regenerative microenvironment. From a clinical perspective, regenerative endodontic procedures aim to balance effective disinfection with preservation of stem cell viability. The use of low-concentration sodium hypochlorite, followed by EDTA irrigation, helps reduce microbial load while promoting the release of embedded growth factors. Minimal or no instrumentation is preferred to preserve dentinal walls and stem cell niches. According to American Association of Endodontists guidelines, induction of bleeding into the canal space or placement of biologically active scaffolds creates an environment conducive to regeneration. This is followed by placement of a suitable coronal barrier and a tight seal to prevent reinfection. Collectively, these strategies reflect a minimally invasive, biologically oriented approach that holds significant promise for achieving true functional regeneration of the dentin-pulp complex rather than mere repair.²⁵

5 | CLINICAL PROTOCOLS: A BALANCE BETWEEN DISINFECTION AND REGENERATION

Contemporary regenerative procedures follow a carefully designed sequence that prioritizes both effective disinfection and preservation of stem cell viability. The use of low-concentration sodium hypochlorite, followed by EDTA irrigation, helps reduce microbial load while simultaneously exposing dentin-derived growth factors essential for tissue regeneration. Unlike conventional endodontic approaches, aggressive instrumentation is minimized to preserve dentinal integrity and maintain stem cell niches within the apical tissues. Subsequently, bleeding is induced into the canal space to introduce stem cells and create a natural biological scaffold. In some cases, alternative scaffolds such as platelet-rich fibrin (PRF), platelet-rich plasma (PRP), or synthetic hydrogels are used to enhance regenerative potential and provide a more controlled environment for tissue growth. Once the scaffold is established, a suitable coronal barrier material is placed to ensure sealing and support regeneration. Mineral Trioxide Aggregate (MTA): MTA is considered the gold standard material in regenerative endodontics due to its excellent biocompatibility, superior sealing ability, and capacity to promote hard tissue formation and cementogenesis. It also exhibits antibacterial properties and encourages favourable healing responses. However, its disadvantages include a long setting time, difficult handling characteristics, relatively high cost, and the potential to cause tooth discoloration, especially in anterior teeth, which can be a significant aesthetic concern. Biodentine: Biodentine, a calcium silicate-based material, has gained

popularity as an alternative to MTA. It offers advantages such as a significantly faster setting time, improved handling properties, and reduced risk of discoloration. Additionally, it demonstrates good biocompatibility and bioactivity, promoting dentin regeneration. On the downside, Biodentine has comparatively less long-term clinical evidence than MTA, and concerns have been raised regarding its mechanical strength and durability over extended periods. Bioceramic Materials (e.g., EndoSequence/TotalFill): Bioceramic materials are increasingly used due to their excellent sealing ability, high biocompatibility, and inherent bioactive properties that stimulate tissue healing and regeneration. They are easy to handle, have favorable flow characteristics, and typically do not cause discoloration. However, disadvantages include higher cost, technique sensitivity in certain clinical situations, and limited long-term clinical data compared to more established materials like MTA. The procedure is completed with a tight coronal seal using appropriate restorative materials to prevent reinfection and ensure long-term success. These steps are guided by recommendations from organizations such as the American Association of Endodontists, although variations in clinical protocols still exist across practitioners due to differences in experience, case selection, and material preference.²⁵

6 | EMERGING ADVANCES IN REGENERATIVE ENDODONTICS

1. Cell Homing Strategies. Cell homing represents a shift toward minimally invasive regenerative therapy. By utilizing chemotactic signals and bioengineered scaffolds, endogenous stem cells are recruited into the root canal system, eliminating the need for laboratory-based cell transplantation. This approach holds significant promise for widespread clinical adoption.⁴
2. Exosomes and Cell-Free Therapies. Recent research has turned toward exosomes—nano-sized extracellular vesicles derived from stem cells. These vesicles carry bioactive molecules, including proteins and RNA, capable of modulating inflammation, promoting angiogenesis, and enhancing tissue regeneration. Their cell-free nature makes them safer and potentially more feasible for clinical translation.
3. Advanced Scaffold Technologies. Innovations in scaffold design include injectable hydrogels, antimicrobial biomaterials, and 3D-bioprinted constructs. These scaffolds can be customized to match canal morphology, support vascular ingrowth, and deliver growth factors in a controlled manner. Such developments are paving the way for personalized regenerative therapies.
4. Platelet Concentrates and Modifications. PRF and its newer variants continue to gain popularity due to their autologous nature and biological efficacy. Enhanced formulations and combinations with other biomaterials aim to improve scaffold stability and regenerative outcomes.
5. Gene Therapy Approaches. Although still in experimental stages, gene therapy offers the potential to directly modulate cellular behaviour by inducing expression of specific regenerative pathways. This could allow precise control over tissue formation in the future.
6. Bioprinting and Tissue Engineering. Bioprinting technologies are enabling the fabrication of pulp-like constructs with pre-designed vascular

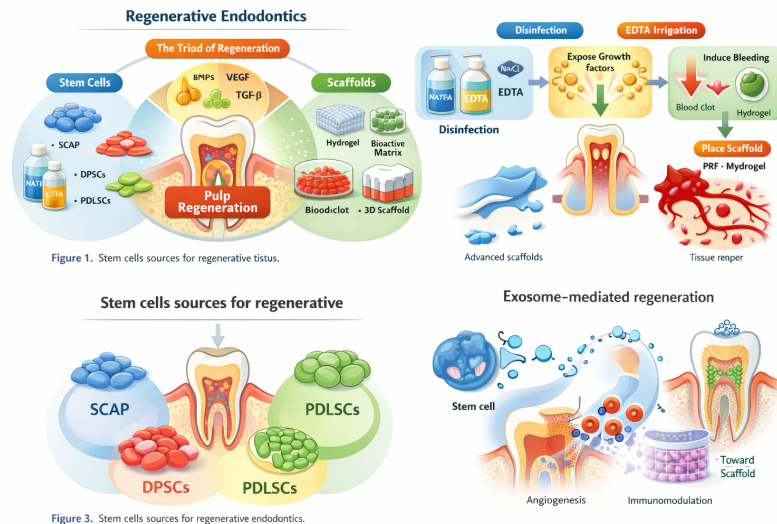


Figure 1. Stem cells sources for regenerative tissues.

Figure 3. Stem cells sources for regenerative endodontics.

FIGURE 1 Tissue Engineering Triad

channels and cellular organization. While currently limited to laboratory research, these innovations may redefine future clinical applications

7 | CLINICAL OUTCOMES AND EVIDENCE

Clinical evidence in regenerative endodontics has shown promising and often encouraging outcomes, particularly in immature teeth with open apices. Numerous studies have reported continued root development, increased dentinal wall thickness, apical closure, and effective resolution of periapical lesions following regenerative procedures. These outcomes not only improve the structural integrity of the tooth but also enhance its long-term prognosis compared to conventional apexification techniques. However, the nature of the tissue formed within the canal space remains variable. While some cases demonstrate the formation of pulp-like tissue with vascular and neural components, others result in fibrous connective tissue or cementum-like deposition, indicating repair rather than true regeneration. Furthermore, the recovery of pulp sensibility is inconsistent, often lagging behind structural healing, which raises important questions about functional restoration. These variations emphasize the need for more standardized clinical protocols, objective outcome assessment tools, and long-term follow-up studies to better understand the true regenerative potential of these procedures.¹⁶

8 | CHALLENGES AND LIMITATIONS

Despite its significant potential, regenerative endodontics is not without limitations. One of the primary challenges lies in the unpredictability of outcomes, as clinical success can vary depending on factors such

as case selection, level of infection and patient-specific biological responses. Achieving an optimal balance between effective microbial disinfection and preservation of viable stem cells within the apical tissues is particularly complex, as excessive use of irrigants or medicaments may compromise the very cells required for regeneration. In addition, issues such as tooth discoloration, intracanal calcification and incomplete tissue organization have been reported in some cases. From a broader perspective, regulatory and ethical constraints pose barriers to the clinical application of advanced strategies such as stem cell transplantation, gene therapy, and tissue-engineered constructs. Moreover, there is still a lack of robust long-term clinical data evaluating the durability, functionality and true biological nature of regenerated tissues, which limits widespread acceptance in routine clinical practice.¹

9 | FUTURE DIRECTIONS

The future of regenerative endodontics is moving toward more refined, integrative and patient-centered approaches that combine biological understanding with technological innovation. Emerging strategies such as hybrid techniques that integrate cell homing with advanced biomaterials are showing great promise in enhancing treatment predictability. The development of patient-specific scaffolds using 3D imaging and bio-printing technologies offers the potential for more precise adaptation to root canal anatomy and improved tissue organization. In addition, exosome-based therapies are gaining attention as a cell-free alternative, capable of modulating cellular responses and promoting regeneration while minimizing immunological concerns. Advances in molecular biology, including the use of targeted growth factors and gene modulation, may further enhance regenerative outcomes. At the same time, improvements in diagnostic tools—such as advanced imaging techniques and the identification of specific biomarkers—will play a crucial role in



FIGURE 2 Clinical Protocol

distinguishing true regeneration from repair, enabling more accurate evaluation of clinical success.¹¹

10 | CONCLUSION

Regenerative endodontics represents a dynamic convergence of biology, technology, and clinical innovation, offering a fundamentally new approach to preserving natural dentition. What was once considered an aspirational concept is now steadily evolving into a viable clinical reality, supported by growing scientific evidence and technological progress. By focusing on restoring vitality rather than simply replacing lost tissue, regenerative therapies have the potential to redefine the goals of

endodontic treatment. Although challenges remain, continued research, interdisciplinary collaboration, and refinement of clinical protocols are likely to enhance both predictability and outcomes. In the near future, regenerative endodontics may transition from a specialized procedure to a standard of care, providing biologically and functionally superior solutions for long-term tooth preservation.

AUTHOR CONTRIBUTIONS

Dr. Ranjini M A: Conceptualization, Methodology, Supervision, Manuscript review & editing; Dr. Divyashri D M: Investigation, Data collection, Formal analysis, Writing – Original draft, Correspondence; Dr. Ashok H K: Methodology guidance, Data interpretation, Review; Dr. Vedavathi B: Supervision, Validation, Final approval; Dr. Priyanka H

Hadimani: Data collection assistance, Literature review; Dr. Nischitha A: Data collection assistance, Literature review

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CONFLICT OF INTEREST

There is no conflict of interest.

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