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Healing from within: Redefining Endodontic Success through Regeneration

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Abstract: Regenerative endodontics represents a transformative approach in managing necrotic or infected pulp in immature permanent teeth by leveraging the principles of tissue engineering—Stem cells, Scaffolds, and Growth factors. Unlike traditional apexification or root canal therapy, regenerative endodontic procedures (REPs) aim to biologically restore the pulp–dentin complex, enabling continued root development and apical closure. This is crucial for immature teeth, which are structurally vulnerable due to thin dentinal walls and open apices. Case selection is critical for REP success, with ideal candidates being patients aged 6–17 years with immature permanent teeth, open apices (>1.1 mm), and no significant systemic health contraindications. Treatment protocols emphasize proper disinfection using low-concentration irrigants and medicaments, followed by scaffold placement (e.g., blood clot, PRF, or PRP) and coronal sealing with biocompatible materials such as Mineral trioxide aggregate (MTA).

The regenerative triad's advancement has led to the development of nanofibrous scaffolds and injectable hydrogels that mimic the extracellular matrix and support cell proliferation and angiogenesis. Innovations include antibiotic-loaded scaffolds, CD31+ and CD105+ stem cells, and mobilized DPSCs, all enhancing the clinical potential of REPs. Furthermore, exosomes and polyelectrolyte multilayer coatings offer novel, cell-free regenerative strategies. Clinically, REPs are particularly valuable in treating immature necrotic teeth where apexogenesis or apexification is impractical. Although current success rates hover around 60–70%, ongoing research into scaffold mechanics, stem cell biology, and biomolecular signaling is expected to optimize outcomes. Regenerative endodontics holds promising implications for preserving tooth vitality, particularly in pediatric dentistry and trauma-related cases.

Keywords: *Regenerative Endodontics, Revascularization, Cell Homing*, *Stem cell, Scaffold, Growth Factors.*

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I. INTRODUCTION

Regenerative endodontics is an evolving field that leverages tissue engineering strategies to revitalize necrotic or infected pulp tissues using the body's intrinsic healing capacity. This paradigm shift from traditional root canal therapy aims to biologically restore the pulp–dentin complex through the interplay of stem cells, biocompatible scaffolds, and signaling molecules[(1,2).] It is especially beneficial for immature permanent teeth affected by pulp necrosis or apical periodontitis, conditions that often halt root development and leave the tooth with open apices and thin dentinal walls. Such anatomical features increase the risk of fracture and compromise the long-term survival of the tooth [(3).]

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Historically, apexification using long-term calcium hydroxide therapy or mineral trioxide aggregate (MTA) has been the treatment of choice for non-vital immature teeth. While these methods induce apical barrier formation, they do not promote continued root development or restoration of pulp vitality. Furthermore, prolonged use of calcium hydroxide has been associated with weakening of the dentin and increased fracture susceptibility [4,5].

In contrast, Regenerative Endodontic Procedures (REPs) offer a biologically driven alternative. By employing scaffold materials such as platelet-rich fibrin (PRF), and promoting cell homing and angiogenesis, REPs facilitate the regeneration of pulp-like tissue, continued root maturation, and apical closure [6]. Additionally, REPs contribute to immune modulation and periapical healing, supporting the return of sensory and protective functions of the dental pulp [7].

Despite some limitations and the need for more standardized protocols, regenerative endodontics presents a promising approach that aligns with minimally invasive, biologically respectful dental care. It represents a significant step toward preserving natural tooth structure and function, especially in young patients with developing dentitions [8].

II. REGENERATIVE TRIAD

Since the advent of tissue engineering in the early 1990s [9], significant progress has been achieved in regenerative endodontics, particularly in developing scaffold-based strategies for the regeneration of dental pulp tissue.

The triad of tissue engineering forms the foundation for regenerative therapy [10]:

- *Stem Cells*
- *Scaffolds*
- *Growth Factors*

- *Stem Cells:*

Stem cells are a unique group of undifferentiated cells with the ability to self-renew and differentiate into various cell types. They are broadly categorized into pluripotent and multipotent cells. Pluripotent stem cells, such as embryonic stem cells, can develop into specialized cells from all three germ layers. In contrast, adult mesenchymal stem cells are multipotent and can only form mesenchymal tissues like bone, dental pulp, and periodontal ligament. These adult stem cells are located in specific tissue regions known as “stem cell niches.” The mesenchymal tissues (e.g., bone, dental pulp, periodontal ligament, etc.) appear to have an enriched population of adult stem cells.

- *Scaffolds:*

Novel biomaterials designed to act as scaffolds have been engineered to support cell adhesion, proliferation, and differentiation [11], and researchers have explored both natural (e.g., collagen) and synthetic (e.g., polylactic acid) polymers in various forms such as nanofibers and hydrogels [12,13]. These scaffolds mimic the natural extracellular matrix (ECM), providing the structural and biochemical cues essential for tissue formation [11,14]. of particular interest are nanofibrous scaffolds, which offer benefits such as high surface area, interconnected porosity, and the ability to guide stem cell behavior at the molecular level [15]. Electrospinning has emerged as a key technique to fabricate such scaffolds, allowing for controlled fiber morphology and drug delivery capabilities [16]. Antibiotic-loaded electrospun scaffolds have been shown to offer antimicrobial activity while minimizing cytotoxic effects on stem cells from the apical papilla (SCAPs) [16].

Additionally, injectable hydrogels like Puramatrix™ have gained attention for their ease of application and ability to form a biocompatible matrix that supports stem cell survival and vascularization in vivo [17].

When combined with dental pulp stem cells (DPSCs) or stem cells from exfoliated deciduous teeth (SHED), these scaffolds have successfully promoted pulp-like tissue formation in animal models [18,19]. Furthermore, experimental strategies using CD31+ or CD105+ stem cell subtypes in combination with bioactive scaffolds have demonstrated promising results in achieving vascularized and innervated pulp regeneration [20].

- *Growth Factors:*

Growth factors are proteins that regulate crucial cellular functions like migration, proliferation, and differentiation, playing a central role in tissue repair and regeneration. While growth factors can naturally originate from blood, pulp remnants, stem cells, or dentin, studies have shown regeneration is also possible without external growth factors. Dentin itself stores nearly 300 proteins, including those that support cellular communication and tissue growth. Proteins such as transforming growth factor Beta 1(tGF-β_1) and platelet-derived growth (PDG) factor enhance cell activity and regeneration. Vascular endothelial growth factor (VEGF) supports angiogenesis, while other growth factor concentrates, often derived from the patient’s blood, significantly promote pulp–dentin complex regeneration in vivo.

III. METHOD

The dental pulp is a soft, vascular, and innervated tissue at the center of the tooth, responsible for dentin formation, nourishment, protection, and sensation. It contains specialized cells like odontoblasts that form dentin and respond to injury. The pulp is organized into layers, including zones with immune and nerve cells that regulate defense and pain. It’s highly sensitive to inflammation due to its confined space and lack of alternate blood supply. Maintaining pulp vitality is essential for tooth development and function, and regenerative treatments now aim to restore lost vitality and sensitivity [21].

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➢ *Cell Homing as a Regenerative Therapy :*

Cell homing is a regenerative approach to rebuild dental pulp by attracting the body's own stem cells into a cleaned root canal. It mimics natural healing by triggering bleeding, which forms a blood clot rich in cells and growth factors. This clot acts as a scaffold, helping stem cells migrate, grow, and differentiate to form new vital tissue inside the tooth [21].

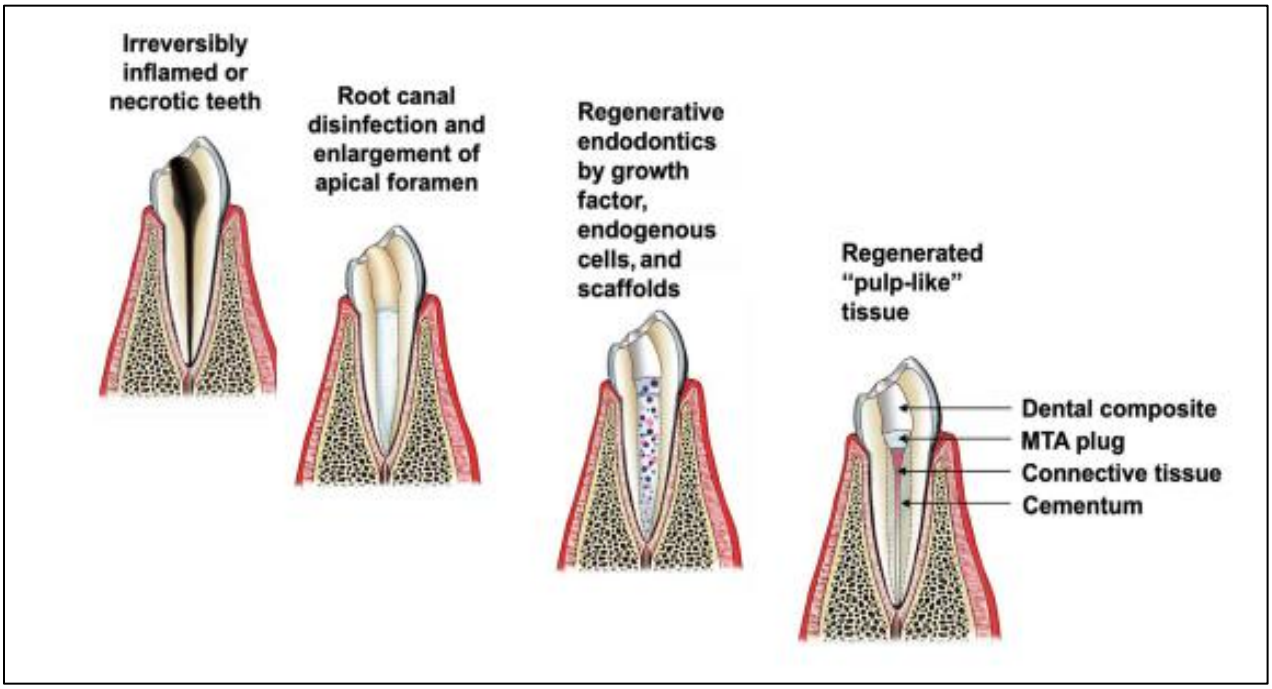

Fig 1 – Schematic Illustration of the Regeneration of the Irreversibly Diseased Dental Pulp Tissue Using Cell Homing Technique. MTA(Mineral Trioxide Aggregate).

IV. CASE SELECTION CRITERIA FOR REGENERATIVE ENDODONTICS

Regenerative endodontic procedures (REPs) such as revascularization and pulp revitalization aim to stimulate the natural development of root structures in immature teeth. Although these biologically based treatments have shown promise, the average success rate remains around 60%, and this variability highlights the critical importance of appropriate case selection to optimize outcomes [22].

- Patient age is a significant factor in determining the suitability of regenerative endodontics. Typically, REPs are recommended for patients between 6 and 17 years of age. This range corresponds with the presence of immature permanent teeth that are still undergoing root development. REPs are contraindicated in primary teeth due to the risk of interfering with the natural exfoliation and eruption of permanent successors [23].
- Tooth anatomy plays an essential role in successful regeneration. Ideal candidates are immature permanent teeth with open apices greater than 1.1 mm in diameter and thin dentinal walls. These characteristics allow for continued deposition of dentin and elongation of roots, strengthening the tooth and enhancing long-term prognosis [3].
- Systemic health conditions also influence case selection. Patients with bleeding disorders, such as hemophilia or von Willebrand disease, or those on anticoagulant therapy, may experience uncontrolled bleeding during the induction of a blood clot. Additionally, systemic conditions like diabetes or immunosuppression can impair healing. In such cases, medical clearance is necessary before proceeding with REPs [24].
- Patient compliance is another key consideration. Regenerative endodontics typically involves multiple visits. Patients who are unreliable or have a history of missed appointments are poor candidates for multi-visit treatments. In such scenarios, a single-visit protocol or an alternative treatment approach should be considered to avoid incomplete therapy and potential failure [25].
- Any acute infection must be resolved prior to regenerative procedures. Clinical signs such as swelling, sinus tracts, or radiographic evidence of periapical pathology indicate active infection, which can compromise regeneration. Proper disinfection and sealing of the canal are prerequisites for a favorable outcome [22,26].
- The diameter of the apical foramen is another vital factor. A minimum width of 1.1 mm is necessary for adequate vascular supply and stem cell migration into the canal. Attempts to artificially enlarge a nearly closed apex are

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discouraged as they carry risks and usually do not provide regenerative benefit [27].

V. TREATMENT PROTOCOL

➢ *First Appointment:*

The treatment protocol begins with the administration of local anesthesia, typically 3% mepivacaine without a vasoconstrictor to avoid constricting blood flow. Disinfection is critical to success and involves isolation with a rubber dam, irrigation with 1.25% sodium hypochlorite, and placement of an intracanal medicament. Either calcium hydroxide or a triple antibiotic paste (metronidazole, ciprofloxacin, and minocycline) can be used as an intracanal medicament, preferably at a concentration of 0.1 mg/mL to reduce cytotoxic effects [28,29].

➢ *Second Appointment (1-4 weeks after 1st visit):*

Reassess the tooth after initial treatment. If infection persists, consider further antimicrobial therapy. Use 3% mepivacaine (no vasoconstrictor), isolate with a dental dam, irrigate with 17% EDTA, dry with paper points, and induce bleeding into the canal using a K-file beyond the apex. Stop bleeding 3–4 mm below CEJ. Place a resorbable matrix if needed, followed by white MTA or calcium hydroxide as a capping material. Cover with 3–4 mm glass ionomer and light cure. Use esthetic alternatives like Biodentine in visible areas. Restore anterior/premolar teeth with RMGI and composite; molars with MTA, then RMGIC[30].

VI. CLINICAL OUTCOMES

According to the American Association of Endodontists (AAE), the success of Regenerative Endodontic Procedures (REPs) is assessed based on specific clinical outcomes:

- The **primary or fundamental objective** is to resolve clinical symptoms and signs, along with radiographic evidence of bone healing.
- The **secondary or preferred outcome** involves the continued development of the root, demonstrated by an increase in root canal wall thickness and/or elongation of the root.
- The **tertiary or additional goal** is the restoration of neural function, indicated by a positive response to pulp vitality tests.

VII. CLINICAL IMPLICATIONS

The management of immature permanent teeth requires a careful differential diagnosis, considering pulp vitality, the extent of root development, and the thickness of dentinal walls. Teeth nearing complete development with thick root walls are generally suitable for conventional treatment, while those with early-stage immature roots and thin dentinal walls are more prone to fracture and are better candidates for regenerative endodontic procedures that encourage continued root maturation and dentin deposition [31].

In cases of pulp necrosis in teeth with relatively thick roots, apexification is a viable option. This involves debridement of necrotic tissue followed by placement of materials like calcium hydroxide, mineral trioxide aggregate (MTA), or bioceramic root repair materials to induce apical barrier formation. MTA and bioceramics have demonstrated superior outcomes, with success rates exceeding 90%, compared to calcium hydroxide, which requires multiple appointments and can weaken dentin over time [32,33].

Apexogenesis is indicated when the pulp remains vital. This procedure preserves healthy pulp to allow natural root development and has shown high success rates, often above 96%[34]. Similarly, Cvek partial pulpotomy removes a standardized 2 mm of pulp tissue and enables root maturation while preserving pulp vitality [35].

Regenerative endodontic procedures (REPs) use biologic approaches such as platelet-rich fibrin (PRF) or platelet-rich plasma (PRP) to promote revascularization in necrotic immature teeth. These methods have shown promising results in apical closure and root elongation, although variability remains in outcomes, highlighting the need for further research [36–39].

VIII. RECENT ADVANCES

Recent investigations in dental pulp tissue engineering have emphasized the significance of scaffold materials, particularly focusing on the comparison between natural and synthetic hydrogels. Galler et al. conducted a pioneering study comparing natural scaffolds like collagen and fibrin with synthetic alternatives, including polyethylene glycol (PEG)-based scaffolds and self-assembling peptides, some of which were functionalized with cell adhesion motifs and enzyme-cleavable sites. Their results demonstrated superior dental pulp stem cell (DPSC) viability and pulp-like tissue formation in natural materials, with fibrin emerging as the most effective scaffold for regeneration [40].

In addition to scaffold development, cell transplantation and cell homing are central strategies for regenerative endodontic therapy (RET). While these techniques show promise, several challenges must be addressed before clinical translation. The mechanisms by which stem cells contribute to neural regeneration remain largely undefined, underscoring the need for lineage tracing and single-cell sequencing to determine the primary cell sources of neurogenesis in RET. Although autologous stem cells help prevent immune rejection, limitations including cell isolation, storage loss, and high costs hinder practical applications. This necessitates the exploration of alternative cell sources and the establishment of stem cell banks [40].

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Natural protein-based gels like fibrin suffer from poor mechanical properties, making them unsuitable for load-bearing applications. To overcome this, interpenetrating polymer network (IPN) hydrogels composed of fibrin and hyaluronic acid-tyramine were developed, offering improved mechanical strength. Further innovations include biomimetic elastin-like recombinant (ELR) scaffolds functionalized with statherin-derived peptides and hydroxyapatite (HAP), which promoted biomineralization, supported DPSC differentiation, and incorporated antimicrobial peptides to combat oral pathogens [40]. Collectively, these multifaceted approaches represent the future direction of RET, where scaffold design, cell signaling, and antimicrobial properties are integrated for effective pulp regeneration.

IX. CONCLUSION

Regenerative endodontics marks a paradigm shift in dental care, focusing on biologically restoring the pulp–dentin complex in immature, necrotic teeth. Utilizing the triad of stem cells, scaffolds, and growth factors, these procedures promote root maturation, apical closure, and pulp vitality. Appropriate case selection—based on age, tooth anatomy, systemic health, and compliance—is crucial for success. Though clinical translation still faces challenges like standardization and cost, advancements in scaffold design and cell-free approaches continue to enhance outcomes. Overall, regenerative endodontics offers a promising, minimally invasive alternative to conventional therapies, with the potential to preserve natural tooth structure and function.

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Conflicts of Interest:
There are no conflicts of interest.

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