Review Article

Advanced Biomaterials in Apexogenesis: A Review

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Abstract Apexogenesis is a vital pulp therapy procedure aimed at preserving pulpal vitality in immature permanent teeth to enable continued root development and apical closure. It is commonly indicated in cases of pulp exposure due to caries or trauma where the pulp remains vital. Traditional materials such as calcium hydroxide and mineral trioxide aggregate (MTA) have demonstrated clinical success; however, their limitations—including poor handling characteristics, discoloration potential, high solubility, and prolonged setting time—have prompted the development of newer biomaterials. Recent advancements include tricalcium silicate–based materials such as Bio dentine, BioAggregate, TheraCal LC, Super MTA Paste, and EndoSequence Root Repair Material (ERRM), which offer improved biocompatibility, enhanced sealing ability, shorter setting times, and better mechanical properties. Calcium phosphate–based materials and natural biomolecules like acemannan further enhance regenerative potential through their osteoconductive and bioinductive properties. Nanotechnology has introduced adjuncts such as silver nanoparticles, graphene-based materials, and hydroxyapatite nanoparticles, which exhibit strong antimicrobial effects while promoting cellular proliferation, angiogenesis, and dentinogenesis. In addition, bioceramic sealers and advanced scaffold systems, including hydrogels and 3D-printed matrices, support stem cell differentiation and controlled growth factor delivery, contributing to more predictable regenerative outcomes. Despite these advancements, challenges such as high cost and limited long-term clinical evidence persist. Future developments in smart biomaterials and tissue engineering are expected to further improve the success and predictability of apexogenesis.

Keywords: Apexogenesis, bio dentine, bio ceramics, Calcium phosphate cement, Nanomaterials, Regenerative endodontics, tricalcium silicate

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INTRODUCTION

Apexogenesis is a vital pulp therapy aimed at preserving the health and function of the pulp in immature permanent teeth, allowing for continued root development and apical closure. The American Association of Endodontics (2013) describes it as a procedure performed to allow continued physiological development and root formation.[1] While the American Academy of Pediatric Dentistry (AAPD 2023) defines it as a histological term describing continued physiologic apex development.[2] Its objectives include sustaining Hertwig's epithelial root sheath (HERS), promoting root end closure dentinal bridge formation at the pulpotomy site, and ensuring continued root development without pathology. Clinically, it is indicated for immature teeth with vital pulp exposure due to caries or trauma, but contraindicated in cases of pulp necrosis, irreversible pulpitis, extensive crown loss, or periapical pathology.[3]

Traditional materials such as calcium hydroxide and mineral trioxide aggregate (MTA) have shown success but also present limitations. Calcium hydroxide demonstrates high solubility, poor sealing, and delayed apical closure, while MTA has drawbacks including handling difficulty, discoloration, and prolonged setting time.[4] These limitations have led to the introduction of newer biomaterials such as Biodentine, bioceramic sealers, and growth factor enriched scaffolds, which provide improved sealing, faster setting, enhanced biocompatibility, and regenerative potential, thereby optimizing the outcomes of apexogenesis. The following section explores the advancements in biomaterials and their role in refining apexogenesis techniques.

A) TRICALCIUM SILICATE-BASED CEMENTS

1. Biodentine

Biodentine is a bioactive calcium silicate–based cement composed primarily of tricalcium silicate, calcium carbonate, and zirconium oxide. Unlike other cements, it is free from calcium aluminate, calcium sulfate, and bismuth oxide. Compared with mineral trioxide aggregate (MTA), Biodentine demonstrates superior mechanical strength, enhanced color stability, easier handling, and a shorter setting time, though its lower radiopacity and occasional difficulties in achieving ideal consistency remain limitations. Biologically, Biodentine releases higher levels of calcium ions and maintains an alkaline pH through hydroxyl ion liberation, which confers antibacterial properties. The initial coagulative necrosis at the pulp interface serves as a protective barrier, while the release of silicon ions has been associated with stimulation of mineralization and dentin bridge formation. Clinical investigations have shown Biodentine to provide outcomes comparable to MTA in direct pulp capping (DPC). However, a recent evidence-based review by Islam et al. (2023) emphasized that MTA has been evaluated in more extensive trials with larger sample sizes, whereas current Biodentine studies involve relatively smaller cohorts. This highlights the need for further high-quality, long-term investigations to comprehensively establish its clinical performance.[5]

Study (Autho r, Year)	Study Design/ Sample	Success Rate (Biodentine vs. MTA)	Follow -up	Key Findings
Hegde et al., 2017.[6]	Clinical evaluati on: carious teeth	83.3% vs. 91.7%	6 months	Both materials are effective; MTA slightly higher success
Awawde h et al ., 2018.[7]	Prospect ive RCT; vital pulp therapy	93.1% vs 93.5% (6 mo); 96% vs 100% (12 mo); 91.7% vs 96% (36 mo)	Up to 3 years	Comparable results; long-term outcomes are dependent on coronal seal and remaining tooth structure

Table 1: Clinical outcomes of Biodentine compared with MTA in pulp capping

2. BioAggregate

BioAggregate is a bioinductive tricalcium silicate–based cement designed to enhance mineralization compared with Mineral Trioxide Aggregate (MTA). Its composition includes tricalcium silicate, dicalcium silicate, monobasic calcium phosphate, amorphous silicon dioxide, and tantalum oxide as a radiopacifier. This unique formulation excludes aluminum and incorporates tantalum oxide instead of bismuth oxide, thereby reducing adverse inflammatory responses and improving biocompatibility. Clinically, BioAggregate demonstrates favorable sealing ability and higher potential for stimulating odontoblastic differentiation and mineralization during pulp capping procedures. Compared with MTA, it is considered a more advanced variant, though evidence remains limited. While studies report homogeneous and thick hard tissue barrier formation, MTA has consistently shown greater levels of thicker hard tissue formation. A recent evidence-based review by Islam et al. (2023) emphasized that, although BioAggregate exhibits promising biological properties and favorable clinical handling, the existing literature is insufficient to fully establish its long-term efficacy in vital pulp therapy. Further well-designed clinical trials are needed before it can be considered a reliable alternative to MTA in pulp capping procedures.[5]

3. Resin-based MTA

TheraCal LC is a light-curable, resin-modified calcium silicate material categorized as the fourth generation of calcium silicate–based cements. It is primarily used for direct pulp capping (DPC) and protective lining. Its formulation enables sustained calcium ion release, which stimulates pulp cell proliferation and differentiation, thereby promoting reparative dentin formation. Clinical evidence suggests comparable short-term efficacy of TheraCal LC to Biodentine and MTA. In a randomized controlled trial involving 90 permanent vital teeth with carious pulp exposure, no statistically significant difference in success rates was observed among TheraCal LC, Biodentine, and MTA after 6 months (Iyer et al., 2021).[8] Similarly, a long-term follow-up study reported success rates for TheraCal LC at 96%, 83%, 73%, and 72% at 1 month, 6 months, 1 year, and 3 years, respectively, compared with 92%, 84%, 80%, and 79% for Biodentine, and 93%, 86%, and 85% for MTA (Peskersoy et al., 2021.[9] According to the study, TheraCal LC's short-term outcomes were promising, but its long-term efficacy is still limited. Most of the studies have recommend that TheraCal LC could be used as a DPC material. However, long-term clinical study is still required for this material.

Super MTA Paste is a resin-modified MTA formulation composed of Portland cement and 4-methacryloyloxyethyl trimellitate anhydride (4-META)/tributyl borane (TBB) resin, which acts as a polymerization initiator. Unlike TheraCal LC, this material does not require light curing. It demonstrates excellent biocompatibility and induces the formation of a uniform dentin bridge, making it a promising candidate for pulp capping procedures. Histological evaluations indicate that its tissue reaction is comparable to TheraCal LC, with favorable pulpal healing and dentin bridge formation. However, comprehensive clinical trials are still lacking. Both short- and long-term studies are required to validate its performance, particularly in comparison with established materials such as Biodentine and MTA. Until such evidence is available, the routine clinical application of Super MTA Paste should be approached cautiously.

4. EndoSequence Root Repair Material (ERRM)

EndoSequence Root Repair Material (ERRM) is a premixed, calcium silicate–based bioceramic designed for vital pulp therapy and root repair. It is available in several formulations: iRoot BP and iRoot BP Plus (iRBP) for apexogenesis, iRoot FS (iRFS) for fast- setting applications, and iRoot SP as a sealer. ERRM contains tricalcium silicate, dicalcium silicate, zirconium oxide, tantalum pentoxide, and calcium sulfate/phosphate, and is free from discoloration-causing bismuth oxide found in MTA, making it more aesthetic in anterior teeth.

Properties Relevant to Apexogenesis

ERRM promotes odontoblastic differentiation and reparative dentinogenesis through enhanced mineralization. iRBP has been shown to increase alkaline phosphatase (ALP) activity and support Bone Marrow Mesenchymal Stem Cell (BMMSC) differentiation via MAPK and autophagy signaling pathways.[10,11] It demonstrates excellent biocompatibility, low cytotoxicity, and supports pulp cell adhesion with minimal inflammatory response.[12] Handling is simplified as the material is premixed and hydrophilic, allowing setting in moist conditions. Reported setting times vary: iRBP (~2 h), ERRM putty (~61–208 min), and iRFS (<1 h).[13] ERRM also provides strong antibacterial activity against E. faecalis, S. aureus, S. mutans, and C. albicans, attributed to its sustained alkaline pH (~12).[14]

Clinical applications

ERRM has been successfully used in direct/indirect pulp capping, pulpotomy, and apexogenesis. In direct pulp capping, it stimulates human dental pulp cell proliferation and tertiary dentin formation. Pulpotomy studies show iRBP produces dentin bridges with well-organized tubules, histologically resembling primary dentin.[15] In apexogenesis, ERRM maintains pulp vitality, promotes root elongation, and forms a stable apical barrier with excellent sealing ability and higher dislodgement resistance compared to MTA.[16]

Comparison with MTA and Calcium Hydroxide

Compared to calcium hydroxide, ERRM offers superior sealing ability, lower solubility, and reduced treatment time. Unlike MTA, which is associated with discoloration, difficult handling, and long setting times, ERRM provides faster setting, better handling, and greater aesthetic stability. These advantages, combined with its biocompatibility and antimicrobial effect, make ERRM a favorable material for apexogenesis and other vital pulp therapies.[17]

B) CALCIUM-PHOSPHATE BASED MATERIALS

Composition and Properties of Calcium Phosphate Cements (CPCs)

Calcium phosphate cements (CPCs) are bioactive materials valued for their biocompatibility and regenerative potential in bone and dentin.[18] They are typically composed of tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrous (DCPA), which react to form hydroxyapatite (HA), the primary mineral of teeth and bone. Their properties can be tailored by modifying the powder-to-liquid (P:L) ratio or incorporating additives such as chitosan, which improves strength, reduces setting time, and enhances durability.[20] The P:L ratio critically influences handling and physical properties: higher ratios increase mechanical strength but may produce a dry, unworkable paste, while higher liquid content improves flowability.[19] CPCs generally set faster than MTA, and acidic chitosan solutions can further accelerate setting by promoting calcium phosphate dissolution.[20]

Advantages of calcium phosphate pulp capping materials

CPCs show superior biocompatibility compared to calcium hydroxide and MTA, with reduced pulpal inflammation and enhanced reparative dentin bridge formation. They are osteoconductive and can serve as carriers for bioactive agents, such as metformin, to stimulate dental pulp stem cells and enhance dentin repair. Unlike MTA, CPCs set through a non- exothermic reaction, making them ideal for local drug delivery. [19]

Acemannan

Acemannan, a bioactive polysaccharide extracted from Aloe vera, has emerged as a promising biomaterial for apexogenesis in immature permanent teeth. Its biocompatibility, biodegradability, and antimicrobial properties make it an attractive alternative to conventional materials such as calcium hydroxide and Mineral Trioxide Aggregate (MTA).

Acemannan promotes pulp healing and dentin bridge formation by stimulating dental pulp stem cells (DPSCs), enhancing odontoblastic differentiation, and upregulating vascular endothelial growth factor (VEGF) expression to support angiogenesis. Its immunomodulatory effects further regulate inflammation, creating an optimal environment for pulp tissue regeneration. Clinically, Acemannan is applicable in direct and indirect pulp capping, pulpotomy, and apexogenesis, providing a biodegradable scaffold that supports continued root development. Unlike MTA, it avoids tooth discoloration while actively enhancing cellular proliferation and tissue repair. By combining antimicrobial protection with regenerative stimulation, Acemannan serves as a dual-function biomaterial, improving healing outcomes in vital pulp therapy and supporting long-term preservation of pulp vitality in immature teeth.[20]

C) BIOCERAMIC SEALERS AND PUTTY

Bioceramic sealers and putty have emerged as promising materials for apexogenesis due to their excellent biocompatibility, bioactivity, and sealing properties. Primarily composed of calcium silicates, calcium phosphate, and zirconium oxide, these materials exhibit unique characteristics that enhance their clinical performance.[21]

A key advantage of bioceramics is their ability to form hydroxyapatite-like crystals upon contact with tissue fluids, creating a bioactive interface with dentin. This promotes pulpal healing and regeneration, improving outcomes in vital pulp therapy for immature permanent teeth.[10] In addition, bioceramics demonstrate high dimensional stability and low solubility, maintaining long-term integrity within the root canal system and minimizing the risk of reinfection compared with conventional calcium hydroxide-based materials.[22] Their alkaline pH also provides antimicrobial effects, supporting pulp preservation and continued root development.

Bioceramics are hydrophilic, allowing them to set in the presence of moisture—an essential property for apexogenesis procedures. Their excellent adaptability to dentinal walls reduces microleakage and enhances treatment prognosis. Commercially available products such as total fill BC Sealer, CeraSeal, and Bio-C Sealer have shown promising clinical outcomes in regenerative endodontics.[23]

Despite these advantages, bioceramic materials have certain limitations. Handling properties can vary among formulations, some require longer setting times compared to traditional alternatives, and their higher cost may limit widespread adoption.[24] Nevertheless, ongoing research and advancements in material science aim to improve usability and accessibility. The development of bioceramic materials represents a significant advance in apexogenesis techniques. While traditional materials such as calcium hydroxide and Mineral Trioxide Aggregate (MTA) are effective, they present limitations including resorption, cytotoxicity, and handling challenges. Bioceramics provide a more predictable, durable, and regenerative alternative, supporting long-term success in vital pulp therapy.[10, 24]

D) NANOMATERIALS IN PULP CAPPING AND APEXOGENESIS

Silver nanoparticles (AgNPs) have emerged as a promising adjunct in apexogenesis due to their potent antimicrobial activity while maintaining pulp viability. They exhibit broad-spectrum antibacterial effects, including against antibiotic-resistant strains, by disrupting bacterial cell membranes, generating reactive oxygen species (ROS), and interfering with DNA replication, ultimately leading to bacterial cell death.[25,26] A key advantage of AgNPs is their sustained antimicrobial activity without compromising the viability of the remaining pulp tissue. Unlike conventional antibiotics, AgNPs reduce the risk of bacterial resistance due to their multifaceted mechanism of action. Their nanoscale size allows deep penetration into dentinal tubules, effectively targeting bacteria in regions inaccessible to traditional agents.[26] Beyond antimicrobial properties, AgNPs demonstrate bioactivity that promotes wound healing and tissue regeneration. They can stimulate fibroblast proliferation, enhance angiogenesis, and exert anti-inflammatory effects, all of which support pulp vitality and continued root development.[27]

Despite these benefits, challenges remain. The long-term biocompatibility of AgNPs is a concern, as high concentrations may exert cytotoxic effects on human cells. Research is ongoing to optimize formulations that balance antimicrobial efficacy with safety. Additionally, integrating AgNPs into existing endodontic materials, such as bioceramics and pulp capping agents, is being explored to further enhance their therapeutic potential.[28]

Graphene-Based Materials

Graphene-based materials have emerged as promising candidates in apexogenesis due to their unique physicochemical properties and biocompatibility. Composed of single or multilayered sheets of carbon atoms in a hexagonal lattice, they exhibit exceptional mechanical strength, bioactivity, and antimicrobial potential.29 These materials support odontoblast differentiation and dentin formation. Graphene and its derivatives, including graphene oxide (GO) and reduced graphene oxide (rGO), enhance proliferation and differentiation of dental pulp stem cells (DPSCs) and act as effective scaffolds for mineralized tissue formation. They also upregulate odontogenic markers such as dentin sialophosphoprotein (DSPP) and alkaline phosphatase (ALP), promoting dentinogenesis.[29,30] Graphene derivatives possess intrinsic antimicrobial properties by disrupting bacterial membranes and generating oxidative stress, reducing the risk of infection during apexogenesis. They also modulate inflammation by downregulating pro-inflammatory cytokines, creating a favorable environment for pulp healing, which is especially beneficial in reversible pulpitis.[30] Despite these advantages, clinical translation remains limited. Concerns include long-term biocompatibility, potential cytotoxicity at high concentrations, and interactions with existing dental biomaterials. Further research is needed to optimize their incorporation into pulp capping agents and scaffolds for apexogenesis.[29,30]

Hydroxyapatite Nanoparticles:

Hydroxyapatite (HA) nanoparticles have gained attention in apexogenesis due to their biocompatibility and ability to mimic the natural mineral composition of dentin and bone. As the primary inorganic component of dental hard tissues, HA plays a crucial role in biomineralization and has been incorporated into various pulp-capping agents to enhance regenerative potential. A key advantage of HA nanoparticles is their ability to improve the mechanical properties of pulp capping materials. When added to calcium hydroxide or Mineral Trioxide Aggregate (MTA), they enhance compressive strength, reduce solubility, and improve overall durability, which is essential for clinical success under masticatory forces.[31]

HA nanoparticles actively promote dentin bridge formation and pulp healing. Their high surface area facilitates calcium and phosphate deposition, accelerating mineralization and forming a protective dentin barrier. They also serve as nucleation sites for hydroxyapatite crystal growth and upregulate odontogenic markers such as dentin matrix protein-1 (DMP-1) and dentin sialo phosphoprotein (DSPP), supporting dentinogenesis and continued root development.

Additionally, HA nanoparticles create a bioactive interface between pulp tissue and the capping material, enhancing cellular adhesion and differentiation. Their release of calcium and phosphate ions contributes to an alkaline pH, providing antimicrobial effects and reducing bacterial colonization at the pulp exposure site. This dual regenerative and antimicrobial action improves the success rate of apexogenesis, particularly in teeth affected by deep caries.[32] Challenges remain in their clinical application, including nanoparticle agglomeration, which can affect uniform dispersion within dental materials, and the need to optimize particle size and concentration for maximal regenerative efficacy.[32]

Regenerative Approaches in Apexogenesis

Regenerative approaches to apexogenesis combine stem cell therapy, growth factors, and advanced scaffolds to promote root development in immature permanent teeth. DPSCs and other MSCs (bone marrow, adipose, SHED) aid regeneration by differentiating into odontoblast-like cells, modulating inflammation, and enhancing angiogenesis. Their action is supported by scaffolds - natural (collagen, fibrin, chitosan) and synthetic (PLA = polylactic acid, PGA = polyglycolic acid) - which provide biocompatible structural support with tunable strength and degradation. Hydrogels, as soft, water-rich, injectable scaffolds, mimic the extracellular matrix and can deliver cells and growth factors in a controlled way, with newer "smart hydrogels" responding to pH, temperature, or enzymes. Key molecules like TGF-β1 and BMPs (BMP-2, BMP-7) drive odontoblast differentiation and dentin bridge formation, with controlled-release systems enhancing localized bioactivity. Newer materials such as Biodentine and Bio-C Repair show advantages over MTA but face cost and evidence limitations. Future directions include nanoparticles, ion-releasing biomaterials, and 3D-printed scaffolds, paving the way for predictable bioengineered pulp–dentin complexes.

CONCLUSION

The evolution of apexogenesis materials has significantly enhanced the prognosis of vital pulp therapy in immature permanent teeth. Traditional materials like calcium hydroxide and mineral trioxide aggregate (MTA) have been widely used; however, newer bioceramic-based materials, silver and hydroxyapatite nanoparticles, and graphene-based formulations have demonstrated superior properties in terms of bioactivity, mechanical strength, and antimicrobial efficacy. These innovations address limitations such as prolonged setting time, discoloration, and cytotoxicity seen with earlier materials. Despite these advancements, challenges such as high costs and the need for long-term clinical validation persist. The future of apexogenesis lies in the development of smart biomaterials with controlled ion release and the integration of 3D-printed bioactive scaffolds for guided pulp regeneration. As research progresses, these cutting-edge materials have the potential to revolutionize regenerative endodontics, ensuring more predictable clinical outcomes and improved long-term tooth survival.

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