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Endodontics

REGENERATIVE ENDODONTICS: REVIEW LITERATURE

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ABSTRACT Regenerative endodontics is the creation and delivery of tissues to replace diseased, missing and traumatized pulp structure of tooth. In this article it is explained about history of tissue damage with replacement of same. Introduction of tissue engineering concept which applies the principle of engineering and life sciences towards development and betterment of tissue functioning. It also includes the engineering triad of stem cells, scaffolds and signaling molecules. With the application of regeneration techniques, limitations, clinical considerations. Regeneration is the modern biological approach for preservation of tissues.

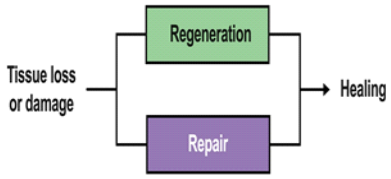
KEYWORDS : regeneration, tissue scaffolds, growth factors, biocompatible material stem cell transplantation

DEFINITION

Regenerative endodontics is the field of dentistry that uses biological techniques to restore the dentin, pulp, and root components of teeth that have been injured.27 The fundamental objective of a regenerative procedure, according to the American Association of Endodontists' (AAE)3 is the eradication of clinical symptoms and signs and the cure of apical periodontitis. Secondary goal include ongoing root maturation and/or thickening of the canal walls.[27]

INTRODUCTION

Injured tissues or lost tissue can heal by tissue regeneration or tissue repair. Repair typically results in the loss of biological function of the wounded tissue since it involves replacing the damaged tissue with new tissue, such as fibrosis or scarring. In contrast, regeneration is the process of using the same cells to replace damaged tissue while also regaining the biological function of the damaged tissue (Slauson & Cooper 2002, Majno & Joris 2004, Kumar et al. 2009).[30]



HISTORY

The word "revascularization" was initially used by Iwaya and colleagues[3] in their endodontic treatment of a developing permanent tooth.[27] It was in 1952 that Dr. Hermann published a case report describing a tooth pulp that had been vitally amputated and had been covered in calcium hydroxide. In addition to the previously mentioned materials, mineral trioxide aggregate (MTA) was also employed to maintain the vitality of the pulp tissues. Procedures like direct pulp capping, partial pulpotomy, apexification, apexogenesis and pulp revascularization are alternatives to apexification for the continued root growth of young permanent teeth.[1]

By producing periapical bleeding in dogs and humans, Nygaard-Ostby[3] attempted to investigate the possibility of regenerating tissue in the partially filled canal area of endodontically treated teeth. This tissue was not pulp-like tissue, but rather fibrous connective tissue and cellular cementum.[3] However, continued root elongation and dentinal wall thickening are unpredictable due to inflammation, infection, or traumatic injury to the Hertwig's epithelial root sheath, which plays a crucial role in root maturation and morphogenesis. Nevins et al[34,35,36] attempted to induce hard tissue formation into pulpless immature teeth with open apex using collagen-calcium phosphate gel in rhesus monkeys.[27,2]

The OBJECTIVES of REPs include

a) primary -resolution of clinical signs/symptoms and periapical bone degeneration and restoration of normal tooth function
b) secondary -stimulating of root maturation
c) tertiary objectives -regeneration of true pulp-dentin complex and the complete restoration of pulpal function.[2]

Depending on whether exogenous cell transfer is involved, the CLINICAL TECHNIQUES of REPs can be divided into cell-free and cell-based procedures.[2]

Cell-free treatments don't use exogenously created cells to regenerate the pulp and dentin in the host. An alternative is to use host-derived bioactive materials, such as blood clots as scaffolds and sources of native cells and growth factors (to encourage the homing of native stem cells from stem cell niches to the site of damage) (i.e., the pulpal space).

Cell-based techniques, in contrast, employ modern tissue engineering techniques as therapeutic treatments in an effort to restore pulp and dentin (e.g., seeding exogenously prepared dental pulp stem cells onto bioactive synthetic scaffolds). A scaffold, also known as a bioactive framework or structural basis, promotes cell adhesion, controls cell proliferation and differentiation, and aids in the development of new tissues.[3]

According to the sources and characteristics of the biomaterials, the biomaterial scaffolds can be categorised as being either host-derived, natural, or synthetic.

1) Host-derived biomaterial scaffolds
a) Blood Clot

Apical bleeding into the canal space induces the formation of a cross-linked fibrin meshwork, which acts as a scaffold for stem cell homing. The cross-linked fibrin meshwork contains vital growth factors for attracting and promoting endogenous stem cell migration, proliferation and differentiation.[2]

The importance of the blood clot in aiding apical periodontitis healing and pulp tissue restoration was first explained by Nygaard-Stby.[3]

NOTE: Before inducing apical bleeding, the American Association of Endodontists advises using 17% EDTA as a last irrigation to release growth factors from dentin and encourage stem cells' biological functions.[3]

Other materials used for hard tissue formation was observed in composite scaffolds, dentin like tissue(2%), cementum like tissue(80%), bone- like tissue(2%)[2]

b) autologous platelet concentrates

In response to activation, platelets immediately degranulate, releasing a burst of growth factors that actively encourage stem cell homing, proliferation, differentiation, and rapid vascularization. Platelet-derived growth factor- transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epithelial growth factor and insulin-like growth factor are among the growth factors that have been released.[3]

Platelet concentrates may be classified into a four-family system

- platelet-rich plasma (PRP), platelet plasma-rich fibrin (PRF)
- leukocyte-and platelet-rich plasma (L-PRP)
- leukocyte-and platelet-rich fibrin (L-PRF)[3]
- The most recent generation of autologous platelet concentrates is concentrated growth factor (CGF)[3]

c) First-generation platelet concentration or PRP was initially launched twenty years ago.

Within 10 minutes of activation, the platelets release 70% of their stored growth factors in a burst and 95% of the release is seen during the first hour. Yet, endogenous clotting factors that reactivate PRP allow for more sustained release of growth factors, which in turn speed up tissue regeneration and repair. Growth factors play a crucial role in stem cell homing and support their biological activities and expedites tissue repair and regeneration[2]

d) Second generation platelet concentration or PRF was introduced in 2001

The PRF has the three essential components for tissue engineering: a fibrin scaffold, continuous release of growth factors, and cells (platelets and leukocytes) that support tissue healing and regeneration. Recent in vitro investigations demonstrated that PRF enhanced stem cells from the apical papilla's (SCAPs) motility, proliferation, and differentiation[3]

According to clinical trials, the application of PRF produced favourable results in the resolution of periapical lesions, root lengthening, thickening of the dentin wall, and restoration of tooth vitality[2]

L-PRP and L-PRF contain higher concentrations of leukocytes compared to PRP and PRF, these cells play a prominent role in the anti-infectious action and immune regulation of the wound healing process[3] Leucocytes in L-PRP and L-PRF produce large amounts of angiogenesis stimulators such as vascular endothelial growth factor (VEGF).[3] In recent years, L-PRF has been used as a biomaterial scaffold in REPs in an immature permanent tooth in association with apical surgery or in autologous DPSCs therapy for a mature permanent tooth with symptomatic irreversible pulpitis.[2] CGF has been used for tissue engineering such as bone regeneration- CGF can promote the proliferation, migration, and differentiation of SCAPs.[3]

e) Decellularized extracellular matrix Cellular extracellular matrix (ECM) generated through tissue decellularization has been used as a natural scaffold in both human and animal dental pulp tissues.[2]
Scaffolds made of natural biomaterials

a) Collagen
Due to its biocompatible and biodegradable qualities, collagen has the potential to be used in tissue engineering. For the regeneration of dental pulp, collagen has been used in pure collagen scaffolds (such as collagen sponge, pellets, and membranes), collagen-based scaffolds combined with other natural or synthetic materials, and composite scaffolds made of collagen, growth factors, or stem cells[2]

By supplying certain cellular markers and homing signals, collagen regulates the biological activities of stem cells in a significant way[2]
3) Alginate, a polysaccharide extract of brown seaweeds, is a naturally occurring salt of alginic acid made by linear copolymers of -(1-4) connected D-mannuronic acid and -(1-4) linked l-guluronic acid monomers.[3]

TGF-containing alginate hydrogels encouraged stem cell differentiation into odontoblast-like cells and enhanced dentin matrix production.[3] Alginate scaffolds with nano-hydroxyapatite added improve their mechanical qualities as well as hDPSC differentiation and biomineralization.[3]

4) Chitosan
Chitosan is a naturally occurring amino-polysaccharide that is generated from the exoskeletons of crustaceans.[2] It contains a random arrangement of -(1-4)-linked D-glucosamine and N-acetyl-d-glucosamine.

Its biocompatibility, biodegradability and wide antibacterial range make it a popular scaffold biomaterial for tissue engineering and drug delivery.

The biological activities of DPSCs are promoted by the conductive and favourable microenvironment provided by chitosan scaffolds.
A simvastatin-releasing chitosan scaffold dramatically improved the chemotaxis and biomineralization capability of dental pulp cells, according to research by Soares and colleagues.[3]

5) Hyaluronic acid
The ECM naturally contains the glycosaminoglycan hyaluronic acid. The morphologic integrity of the dental pulp is preserved, extracellular space is maintained and the dentin and enamel matrix are modulated throughout odontogenesis.

A hydrogel made of hyaluronic acid can be injected into the root canal.The interaction between hyaluronic acid and the SCAPs' membrane receptors speeds up their migration into the canal space.
6) Synthetic biomaterial scaffolds

a) Hydraulic cements made of calcium silicate.
Tricalcium silicate-based materials having hydraulic and hydration capabilities are known as hydraulic calcium silicate cements.

The first-generation hydraulic calcium silicate cement - mineral trioxide aggregate (MTA), was introduced to endodontics in the 1990s.
b) Synthetic polymers

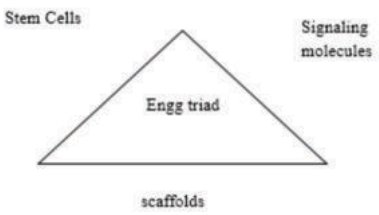
The synthetic polymers polylactic acid (PLA), polyglycolic acid (PGA), poly-l-lactic acid (PLLA) and polylactic-glycolic acid have all been employed successfully as scaffold materials in pulp tissue engineering (PLGA)

In order to maintain the health of DPSCs and periodontal ligament stem cells, polylactic acid has been successfully employed to build dental pulp and periodontal constructions[4]

c)Hydrogels
Since they are simple to utilise and can adapt to irregularly shaped root canal systems, injectable biomaterials such hydrogels are of special relevance for creating scaffolds in REPs[5]. Several acellular or cell-filled constructions that can be injected into human dental root segments created through GelMA-based hydrogels Gelatin methacryloyl (GelMA)

Tissue engineering and regenerative medicine - TERM
Mason and Dunnill state that the goal of regenerative medicine is to replace and regenerate human cells, tissues or organs.To restore tissues or organs, tissue engineering uses engineering ideas based on cells, scaffolds, and bioactive chemicals.[42]

A rapidly expanding scientific discipline called tissue engineering combines the ideas of biology, engineering, and medicine to replace, repair or regenerate tissues that have been damaged or destroyed due to illness or trauma.[5]



Source of Stem cells:

a)Dental pulp stem cells (DPSCs) are clonogenic cells having a strong proliferative potential and a capacity for long-term self-renewal.[5] It depends on the interaction of growth factors, extracellular matrix proteins, receptor molecules, and stem cells for them to reside in niches in pulp chambers.

b) Miura et al. isolated stem cells from exfoliated deciduous teeth (SHED), which showed multipotential differentiation characteristics and higher cell population doublings than DPSCs.[5]

c)Stem cells from apical papillae (SCAP): Sonoyama et al. made the initial discovery of MSC-like cells in the tooth root apex.[5]
d)Periodontal ligament stem cells (PDLSCs): These multipotent cells have the capacity to differentiate into adipocytes, chondrogenic cells, and cementoblast-like cells[5].

e)Dental follicle precursor cells (DFPCs): Localized in a dental sac, also known as a dental follicle, a loose connective tissue that surrounds developing teeth and also impacted teeth[5]

Tissue regeneration requires the appropriate signals (growth and differentiating factors) that activate these cells[5]

growth factors such as
a)fibroblast growth factors (FGF)
b)platelet-derived growth factor (PDGF)
b)epidermal growth factor (EGF)
c)insulin-like factor (IGF)[5]

growth factors like PDGF, TGF, IGF-1, EGF, and FGF may participate in dentin regeneration processes when damage occurs[84] during tooth formation and regeneration growth factors involved are vascular endothelial growth factor (VEGF) and bone morphogenetic protein (BMP)[5]

Scaffold
There are various types of scaffolds –
a)based on their origin; natural scaffolds (e.g., collagen, hyaluronic acid, PRF, PRP, blood clot, chitosan)
b) artificial scaffolds (e.g., polymers of polyglycolic acid, polylactic acid, polyepsiloncaprolactone, glass–ceramic, and bioactive glasses)[5]

Application:
1. Calcium hydroxide and Mineral Trioxide Aggregate (MTA) apexification are traditional therapies for necrotic, developing permanent teeth.[21]
2. TAP (triple antibiotic paste) is successful in cleaning necrotic infected pulps and it provides an environment that is conducive to the regeneration of vital tissue. It is also reported that dentin thickness is increased.
3. Promote apical healing
3. immature tooth with apical periodontitis
4.Continue root maturation in necrotic pulp
5. Mineralize the dentinal walls to strengthen the tooth against fracture
7. its prospective therapeutic approach for halting type 1 external root resorption

LIMITATIONS:
1. RET was deemed unsuccessful in certain cases due to tooth discolouration, recurrent cavities, crown breakage, or loss of coronal restoration.
2. Dens evaginatus (30%) and dental trauma compromised 59% of the instances, both of which could cause root resorption and injury to the apical papilla and the Hertwig epithelial root sheath, which could result in the RET failing.
3. Persistent periapical radiolucency and the absence of thicker root walls[20]

CLINICAL CONSIDERATIONS:
1. Surface and structural changes in dentine micro hardness have been observed after using chelating agents such as 3%, 10%, 17% EDTA, and 10% citric acid. This has an impact on the inorganic collagen content as well as the micro hardness of dentine surfaces.[10]

2. In regenerative research, 17% EDTA influences fibrin development along with blood clot formation, whereas saline solution use may enhance fibrin formation.[12]

3. The use of drugs in regenerative endodontics shown that Cefaclor reduced the microhardness of dentin more than triple antibiotic paste, amoxicillin + clavulanic acid did at a depth of 1,000 m, although the pastes offered comparable adhesion for MTA placement[11]

4. PBS (phosphate- buffered saline) treatment of leftover EDTA increased cell viability on the dentin surface during regeneration. Moreover, ultrasonic activation improved the biological effects and growth factor release.[13]

5. The organic dentine matrix is denatured by the use of calcium hydroxide with an alkaline pH, and the application of double antibiotic paste exposes the collagen-rich dentin matrix.[15] By producing hydroxy carbonate apatite crystals that destroy the dentinal tubules and protect the dentine, bioactive glass raises the micro hardness of dentine between 4 to 12 weeks. This prevents demineralization and promotes remineralization.[15]

6. Regenerative endodontic materials might cause tooth discoloration; to lessen the impact, seal the dentin bonding agent before applying disinfectant paste and barrier materials should be considered[22]

NEWER APPROACH:
1) Dentin-like constructions inserted with boron (B) modified bioactive glass nanoparticles (BG-NPs)

present a new technique for dental tissue engineering applications. These three-dimensional scaffolds feature tubular morphology for dentin regeneration[16].

2) Hypoxic circumstances can modify the production of inflammatory cytokines/factors by mesenchymal cells in vitro, taking use of the natural healing abilities of host cells in dental pulp and the periapical complex. In order to reduce pulpal inflammation and provide a favourable microenvironment for the regeneration of the dentin-pulp complex, hypoxia-induced SHED cell products may be helpful.
3) Dedifferentiation of somatic cells into regenerative cells may result from the temporary inactivation of the tumor-suppressor genes Arf and Rb in human post-mitotic somatic cells (Pajcini et al.2010)

CONCLUSION
In order to sustain root development, strengthen the dentinal walls, and revive a tooth's dental pulp, dentists utilise regenerative endodontic procedures (REPs). This helps to avoid the tooth from being lost in the future. Vital pulp therapy's effectiveness is influenced by the patient's age and stage of root growth in addition to the blood supply (Mjor 2002; Hsted Bindslev & Lvschall 2003).[30] As a result of bacterial biofilms adhering to the irregular surface of the blunderbuss canals, standard debridement and disinfection in root canal systems is extremely difficult, making microbial treatment of necrotic immature teeth with apical periodontitis hard. regeneration of new tissue with physiological properties similar to the native pulp-dentin complex at the histologic level; nonetheless, this seems an implausible result of present regenerative technologies.

Dentists should be able to determine the vitality status of damaged dental pulp and should follow protocol. With revascularization, every precaution should be taken to ensure that the environment is sterilised and that materials are applied, handled, delivered, and followed up on for better outcomes. Future dentists will be bioengineers capable of producing a wide range of replacement tissues for their patients, as the future of dentistry makes abundantly evident and unavoidable.

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