Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

IS IT CURRENTLY POSSIBLE TO REGENERATE THE PULP IN MATURE PERMANENT TEETH WITH IRREVERSIBLE PULPITIS OR NECROSIS? AN UP-TO-DATE LITERATURE REVIEW

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ABSTRACT

Introduction: The “gold standard” to treat mature teeth with irreversible pulpitis or necrosis is root canal treatment (RCT), however by removing the pulp tissue, the tooth loses its vital functions. Regenerative endodontic therapy (RET) aims to restore these functions. While successful in immature teeth, RETs have recently been applied to mature teeth using pulp engineering, stem cells, scaffolds and growth factors; **Objectives:** to assess pulp tissue regeneration in mature teeth with irreversible pulpitis or necrosis; **Material and Methods:** An online literature review was conducted using PubMed, MedLine, manual searching in the “Revista Oficial de Endodoncia Española” (AEDE) and articles reference lists. References were exported via Zotero™ and limited to English and Spanish articles on mature permanent teeth from 2015 onwards; **Results:** 15 articles met inclusion and exclusion criteria, including 3 case series, 3 clinical cases, 4 randomized trials, 2 randomized studies, 2 retrospective case studies, 1 randomized control study; **Conclusions:** RETs show promising outcomes in mature teeth, although there is not sufficient evidence demonstrating its effectivity on a long-span period (> 5 years). Periapical bleeding is the primary technique to obtain cells and factors for tissue regeneration. Bacterial clearance and coronal sealing are essential for success. Further studies are needed to determine whether RETs can replace RCTs in mature teeth.

KEYWORDS

Dentistry; Endodontics; mature permanent teeth; irreversible pulpitis; necrosis; pulp regenerative therapy.

RESUMEN

Introducción: El tratamiento de conductos radiculares (TCR) es el "gold standard" para tratar dientes maduros con pulpitis irreversible o necrosis, pero al eliminar tejido pulpar, el diente pierde sus funciones vitales. La terapia endodóntica regenerativa (TER) busca restaurar estas funciones, aplicándolas solo recientemente en dientes maduros, usando ingeniería de pulpa, células madre, andamios y factores de crecimiento; **Objetivos:** Evaluar la regeneración del tejido pulpar en dientes maduros con pulpitis irreversible o necrosis; **Material y Metodos:** Se realizó una revisión bibliográfica usando PubMed, MedLine, búsqueda manual en la "Revista Oficial de Endodoncia Española" (AEDE) y bibliografía de artículos, exportando las referencias mediante Zotero™. Se consideraron artículos en inglés y español sobre dientes permanentes maduros desde 2015; **Resultados:** 15 artículos respetaron los criterios de inclusión y exclusión: 3 series de casos, 3 casos clínicos, 4 ensayos aleatorizados, 2 estudios aleatorizados, 2 estudios retrospectivos y 1 estudio controlado aleatorizado; **Conclusiones:** Las TER muestran resultados prometedores en dientes maduros, aunque no hay suficiente evidencia que demuestre su efectividad a largo plazo (> 5 Años). El sangrado apical se usa para obtener células y factores para la regeneración. La eliminación bacteriana y el sellado coronal son esenciales. Se necesitan más estudios para determinar si las TER pueden reemplazar los TCR en dientes maduros.

PALABRAS CLAVE

Odontología; Endodoncia; dientes permanentes maduros; pulpitis irreversible; necrosis; terapia regenerativa de la pulpa.

Contents

1. INTRODUCTION

The pulp is a highly vascularized and innervated connective tissue that is found inside the tooth beneath the dentin (1). It runs along the root up to the crown (2,3).

It contains various cell types (such as odontoblasts, fibroblasts, histiocytes, mast cells, macrophages and plasma cells) essential for the development of the tooth's tissues, defense mechanisms and the tooth's nutrition. Besides cells, the pulp is also formed by connective tissue, made mainly of collagenous fibers, and ground tissue (2).

The pulp has four main functions: formative, nutritive, sensorial and defensive (4,5).

1.1. Irreversible pulpitis

Irreversible pulpitis is an inflammation that blocks regenerative or healing processes, hence the use of the term "irreversible", of the pulp tissue (3). While it is often caused by caries, It may also be caused by other stimuli such as traumas (6).

It is divided in symptomatic and asymptomatic. Typically, the symptomatic irreversible pulpitis is characterised by a sharp, constant pain, that is triggered by a stimuli, such as cold and hot temperatures, consuming sweets and laying down (6).

It is diagnosed by vitality tests performed over the affected tooth that show increased positivity (the pain is very acute, and it doesn't stop if the stimulus stops) (4).

Normally, irreversible pulpitis is treated by performing root canal treatment (RCT). If it is not treated, the pulp will eventually become necrotic (4).

1.2. Necrosis

Necrosis refers to the partial or complete death of the dental pulp due to insufficient or lost blood supply (5). In mature permanent teeth, the protocol followed in case of necrosis is to perform a RCT. If pulp necrosis is not treated, it can lead to more problematic consequences (7).

1.3. Endodontics and root canal treatment

Endodontics is the branch of dentistry that is related to the management of the pulp. Its main objective is to preserve a natural tooth in case of any kind of damage (8).

The most studied and currently performed treatment in this area is the RCT. It consists of removing the infected pulp and disinfecting the root canals to create a sterile environment as much as possible. The root canal is then sealed with biocompatible materials such as Gutta Percha (9).

1.4. Endodontic Regenerative Therapy

While RCTs are largely successful in treating irreversible pulpitis and necrosis, the tooth does loses its pulp and, as a result, lacks its nutritive and defensive mechanisms (10). Therefore, a devitalised tooth is weaker and more prone to fractures and new infections. Regenerative Endodontics Therapy (RET) tries to find solutions to this condition and to save a tooth's pulp. To achieve this objective, RET uses an engineering triad (stem cells, biomimetic scaffolds and bioactive growth factors) to achieve regeneration of the pulp tissue (11).

The use of bioactive materials aims to enhance the formation of odontoblast-like cells, that can differentiate into odontoblasts and make more dentine, and act to maintain pulp homeostasis (12).

In order to have the differentiation of cells and the formation of new tissue, it is essential to have a favourable microenvironment with a correct interaction among cells (13). These conditions can be created thanks to the use of different scaffolds that support the retention, proliferation, migration and organization of the new cells (14).

1.5. Pulp engineering

Pulp engineering is a field of endodontics where the main objective is to find new techniques with satisfactory results in pulp regeneration (15).

The principal materials used in pulp engineering are stem cells, signeting molecules and materials to be used as physical scaffold, such as Platelet-rich plasma (PRP) and platelet-rich-fibrin (PRF). PRP and PRF are autologous derivatives from blood that are used due to their ability of inducing tissue regeneration (15,16).

There are different kinds of dental stem cells depending on their origin: from the apical papilla of immature permanent teeth (SCAP), that form new dentin at the level of the root (17); from the pulp of a permanent tooth (DPSCs), that form dental pulp-like tissue (15).

1.6. Historical background

RET was first used in 1961 by Nygaard Östby, who studied the potential regenerative effect of blood clot formation inside the root canal after an over-instrumentation. Östby referred to this therapy as revascularization (18). The American Association of Endodontics (AAE) defined RET or revascularization as procedures that are biologically based, where their objective is to restore dental tissues that are damaged (19). In 2001 the method of revascularization was first used and described by Iwaya et al. 2001 in a clinical case of an immature premolar that was necrotic. After the treatment, the outcome showed root maturation and thickening of root canal walls (20).

Immature permanent teeth do not have a fully developed root, leaving the apex open and divergent on X-rays (16). An open apex increases the risk of infection spreading from the pulp to the periapical tissues. However, it also provides better access to SCAP, which can help regenerate both the pulp and the incomplete apex (21).

In 2000, dental pulp stem cells in permanent teeth (pDPSC) and, in 2003, dental pulp stem cells in deciduous teeth (dDPSC) were discovered respectively. A new era for regenerative procedures started (17,22). Clinicians began to relate the term "revascularization" with RET procedures using calcium hydroxide as intracanal medication. Although its use has been later questioned, CaOH remained the cement of choice as medication (23). The use of a new material, mineral trioxide aggregate (MTA), was studied in the early 2000s. From 2006 onwards, it was preferred because of its excellent sealing properties and support for new tissue growth (24).

Hoshino et al. 1996 proposed a paste formed by ciprofloxacin, metronidazole and minocycline that was widely used by clinicians (25). After a study by Banchs & Trope, it became known as triantibiotic paste, and it continued to be used as disinfection system during many years (26).

The studies of stem cells and BioRoot (MTA based cement) engineering continued in immature teeth aiming to develop a protocol that could likely replace the use of dental implants, form new bone and induce hematopoietic marrow elements, as well as allowing the development and maturation of the apex (21).

In 1996 Mooney et al. pioneered new systems in the pulp tissue engineering and the use of biocompatible materials and chemicals in dentistry (27). An article published in 2008 showed how the studies of stem cells, scaffolds and growth factors (GF) improved the success of regenerative endodontics (21). PRP was found to be a good option as scaffold material (28,29), with its first clinical use reported by Torabinejad M. et al. 2011. RETs have continued to advance with higher success rates and new scaffolds materials, such as polylactic acid (PLA) , have been introduced (30). In 2018, the AAE protocol included autologous materials like blood clots, PRF, PRP and autologous fibrin matrix (AFM) for immature teeth with necrosis (31).

1.7. Current state of the subject

While initially reserved for immature teeth, recently, RET techniques have been applied to mature teeth with irreversible pulpitis or necrosis. The treatment yielded surprising results, including regeneration of proprioception and the immune system (32).

Although there is a need for more studies on mature teeth, recent meta-analysis suggest that RET in teeth with closed apex and a pulp pathology could be a feasible alternative to

conventional RCTs (33,34). The difference between mature and immature permanent teeth is that the first has its apex closed and the root is fully developed (35).

Scelza et al. 2021 carried out a meta-analysis of studies comparing clinical and radiographic outcomes of mature teeth with necrotic pulp before and after REP, where RCT was used as control group. The results were positive to REP, but further clinical studies are needed to confirm RET's role as a definitive alternative to RCT (34). Other studies have confirmed RET as a likely alternative option to the conventional treatments used in endodontics (33,36,37). However, it is true that mature teeth have less stem cells than immature teeth due to the closed apex, resulting in a more difficult communication between the pulp and the SCAP (38). Cases where the RET's outcome is negative are also described and detailed studies on the contributing factors are still required (39).

1.8. Justification

RCT has been used to preserve natural teeth in the mouth and has avoided resorting to the need of extractions and implant placement in many cases, becoming the "gold standard" treatment in endodontics. However, the functions of the pulp are essential for the teeth. RET restores the pulp-dentin complex, making it an alternative to RCT and the disadvantages that it brings, such as root fractures or reinfections. While RET has been tested and confirmed as a good alternative on immature permanent teeth, more research on mature permanent teeth is still needed before it can be identified as the treatment of choice in cases of irreversible pulpitis or necrosis.

2. OBJETIVE

To analyze according to the literature if it is possible to regenerate the pulp of mature permanent teeth in case of irreversible pulpitis or necrosis at present.

3. MATERIALS AND METHODS

An electronic search of the Medline and PubMed was conducted in October 2024. The literature search was extended by manual searching in the AEDE, la Revista Oficial de Endodoncia Española. Another manual searching was made from the reference lists of the essential articles. All references were exported with the use of free software Zotero™ software (Vers. 7.06).

This study is focused on mature permanent teeth with irreversible pulpitis or necrosis and regenerative treatments that can bring the pulp back to a normal response and functions. A total of 15 articles were studied.

The selection of articles was based on eligibility criteria:

Inclusion criteria

Articles in English and Spanish were considered starting from the year 2015 for the results section to have more homogeneous and relevant data.

Studies on mature permanent teeth with irreversible pulpitis and / or necrosis.

Studies that were: randomized clinical trials, cohort studies, case series, clinical cases and case reports.

Sample: adult and adolescent individuals.

The selected articles presented data with sufficient bibliographical references.

Exclusion criteria

Articles before 2015.

Articles about immature permanent teeth.

Articles on mature permanent teeth that did not allow complete access were excluded.

Studies on mature permanent teeth with reversible pulpitis.

Studies over animals were also excluded.

In vitro studies.

Studies that were: systematic reviews and narrative reviews.

Studies with no relevant conclusions on the topic of research.

SEARCH STRATEGY

IDENTIFICATION OF SEARCH TERMS

In patients with mature permanent teeth with irreversible pulpitis or necrosis, how does pulp regenerative therapy compared to root canal treatment and regenerative procedures on immature teeth affect the regeneration of the pulp-dentin complex and the return of neurogenesis?

*Key words: in English and then translated to Spanish

EN: Adolescents; adults; mature permanent teeth; irreversible pulpitis; necrosis; pulp regenerative therapy; root canal treatment, pulp-dentin complex, neurogenesis.

ES: Adolescentes; adultos; dientes permanentes maduros; pulpitis irreversible; necrosis; terapia regenerativa de la pulpa; endodoncia; complejo pulpo-dentinario; neurogénesis.

SEARCH EQUATION

The following equations were used for the search in the data-source Pubmed in English.

- (((dentistry) AND (tissue engineering)) AND (scaffolds)) AND (mature teeth)
- (((irreversible pulpitis[MeSH Terms]) OR (pulp necrosis[MeSH Terms])) AND ((mature permanent teeth[MeSH Terms]) NOT ((immature permanent teeth[MeSH Terms]) OR (open apex[MeSH Terms]))AND (REGENERATIVE ENDODONTICS)
- (((((dentistry) AND (mature teeth)) AND (irreversible pulpitis)) OR (pulp necrosis)) NOT (immature teeth)) NOT (open apex)
- (((((((dentistry) AND (mature teeth)) AND (irreversible pulpitis)) OR (pulp necrosis)) NOT (immature teeth)) NOT (open apex)) AND (tissue engineering)) AND (scaffolds)
- (((dentistry) AND (pulp regenerative techniques)) AND (mature teeth)) NOT (immature teeth)

The equations were adapted and applied to the other data sources following their own specifications. The same process was conducted in Spanish.

The review was managed in accordance with the PRISMA statement (40). The searching and selection processes are demonstrated in the flow chart in Figure 1.

All included clinical trials were independently assessed for the risk of bias.

4. RESULTS

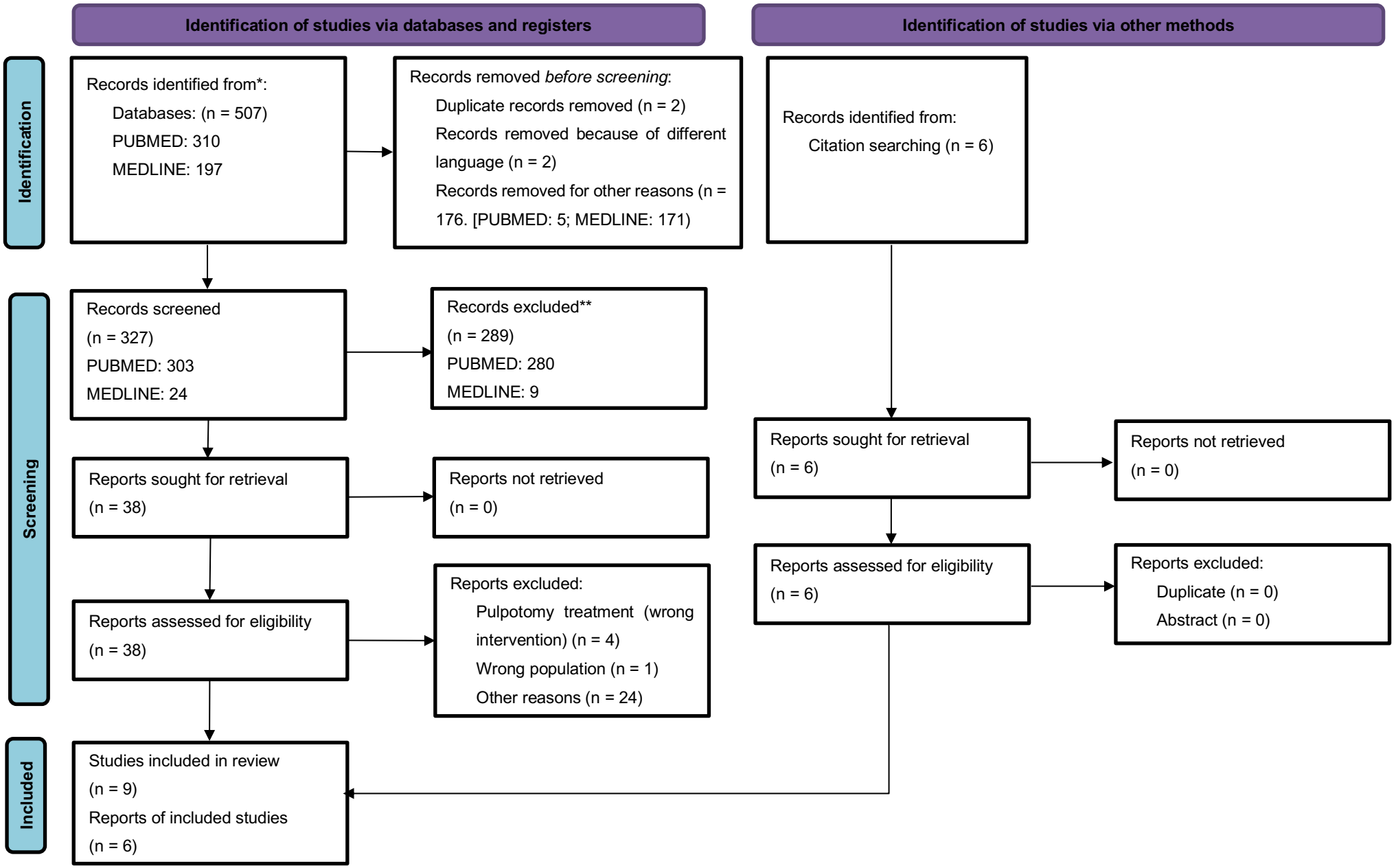

Figure 1. Flow chart of the literature search. (40)

The types of articles that were analysed are shown in the following table [Table 1]:

Table 1. Study types.

NUMBER	AUTHOR	STUDY TYPE
1	Saoud et al. 2016 (41)	Case series
2	Nagas et al. 2018 (42)	Clinical case
3	Samra et al. 2018 (43)	Case series
4	Nageh et al. 2018 (44)	Clinical study
5	Jha et al. 2019 (45)	Randomized clinical trial
6	Arslan et al. 2019 (46)	Preliminary randomized clinical study
7	Meza G et al. 2019 (47)	Retrospective case study
8	El-Kateb et al. 2020 (48)	Randomized control clinical trial
9	Brizuela et al. 2020 (49)	Randomized control clinical trial
10	Feitosa et al. 2021 (50)	Randomized control study
11	Mittal et al. 2021 (51)	Randomized clinical trial
12	Aguilar et al. 2021 (52)	Clinical case
13	Lu et al. 2023 (37)	Retrospective study
14	Al-Rawhani et al. 2024 (7)	Randomized control clinical study
15	Brizuela et al. 2024 (53)	Cases report

As shown in table 1, different types of studies were analysed: 3 case series studies, 3 clinical case studies, 4 randomized clinical trials, 2 randomized clinical studies, 2 retrospective case studies, 1 randomized control study.

The main characteristics of these 15 articles are resumed in the following table [Table 2]:

Table 2. Authors and title of the articles; sample size; brief description of the procedures and the main materials used; materials useful for RET.

Author	Sample	Procedure and Materials	CaOH/Silicate Cement/PRP/Stem cell…
Saoud et al. 2016 (41)	Patients: 6 (4F + 2M) Age: 8-21 yo Teeth: 7 (3 anterior + 4 molars) Pathology: necrotic pulp with apical periodontitis Aetiology: 3 caries, 4 traumas	Chemomechanical debridement and use of Metapaste. Overinstrumentation. Anaesthesia: 2% lidocaine with 1:100,000 epinephrine	MTA sealed with composite or amalgam.
Nagas et al. 2018 (42)	Patients: 1 F Age: 21 yo Teeth: 2 incisors Pathology: necrosis with apical periodontitis Aetiology: trauma	Triantibiotic paste (ciprofloxacine, metronidazole and clindamycin). 4 weeks after, removal of the paste and overinstrumentation. Anaesthesia: 2% lidocaine with 1:100,000 epinephrine	White MTA and Glass Ionomer cement (GIC) and composite.
Samra et al. 2018 (43)	Patients: 3 Age: 20-30 yo Teeth: 3 incisors Pathology: necrosis with apical periodontitis Aetiology: trauma	Triantibiotic paste. After 3 weeks, Overinstrumentation. Anaesthesia: 3% mepivacaine no vasoconstrictor	MTA and GIC and composite.
Nageh et al. 2018 (44)	Patients: 15 Age: 18-40 yo	Double antibiotic paste (metronidazole 500mg and ciprofloxacine 500mg).	Temporary GIC. Platelet Rich Fibrin (PRF).

	Teeth: upper central incisors Pathology: necrosis with apical periodontitis Aetiology: caries/trauma	3 weeks after overinstumentation. Anaesthesia: 2% lidocaine with 1:100,000 epinephrine	White MTA.
Jha et al. 2019 (45)	Patients: 30 Age: 9-15 yo Teeth: upper incisors and multirooted teeth (ex: lower first molar) Pathology: necrosis with apical periodontitis Aetiology: caries/trauma	Triantibiotic paste. SealBio technique (group I) and MTA (group II). Overinstrumentation. Anaesthesia: 3% mepivacaine no vasoconstrictor	Calcium sulphate-based cement (Cavit G) with coronal restoration. SealBio vs MTA.
Arslan et al. 2019 (46)	Patients: 49 Age: 18-30 yo Teeth: 56 upper and lower uniradicular teeth Pathology: necrosis with apical periodontitis Aetiology: caries/trauma	One group: instrumentation and gutta percha Another group: same instrumentation but with the use of triantibiotic paste for 3 weeks. Overinstrumentation. Anaesthesia: - RCT: 4% articaine with 1:200,000 epinephrine - RETs: 3% isocaine no vasoconstrictor	Calcium hydroxide (CaOH) paste for 1 week. Second group: MTA and composite resin.
Meza et al. 2019 (47)	Patients: 1 M Age: 50 yo Teeth: 44	Pulp removal with sterile pulp extractor, placed in phosphate-buffered saline (PBS) solution, 2 mL penicillin/streptomycin and 250 mL 80 mg/mL gentamicin.	CaOH capsule mixed in a sterile glass slab with sterile saline. Biodentine to seal the canal. GIC and then composite resin.

	Pathology: symptomatic irreversible pulpitis with normal apical tissue Aetiology: caries	Pulp tissue cleaning and enrichment with 10% fetal bovine serum for 1 week. Overinstrumentation and PRF clot introduction. Collagen CollaPlug placed over. Anaesthesia: - 1st visit: 2% hydrochloride with 1:80,000 epinephrine - 2nd visit: 3% mepivacaine no vasoconstrictor	
El-Kateb et al. 2020 (48)	Patients: various Age: 20-34 yo Teeth: 18 (17 central incisors + 1 lateral) Pathology: necrosis with apical periodontitis Aetiology: trauma/defective restorations	9 teeth treated with REPs with rotary instruments (PTN) until size X3. 9 (control group) treated with REPs using files until X5. Bleeding induced. Anaesthesia: - 1st visit: 2% lidocaine with 1:100,000 epinephrine - 3% mepivacaine no vasoconstrictor	CaOH until the second visit. Biodentine.
Brizuela et al. 2020 (49)	Patients: 36 patients (25 F + 11 M) Age: 16-58 yo Teeth: incisors, canines and mandibular premolars Pathology: necrosis with apical periodontitis	Preparation pf the Platelet Poor Plasma (PPP); collection of umbilical cords cells; encapsulation of the UC-MSCs in the PPP. Gelatin sponge hemostat (Gelita Medical GmbH) was then placed on the cervical third of the tooth to contain the Biodentine. Anaesthesia: N/A	CaOH paste Biodentine.

	Aetiology: N/A		
Feitosa et al. 2021 (50)	Patients: 3 patients (2 M + 1 F) Age: 18-40 yo Teeth: infected uniradicular premolar Pathology: necrosis with apical periodontitis Aetiology: caries/defective restoration	Instrumentation of the premolar and extraction of a third molar. No apical bleeding. Preserved pulp tissue of third molar introduced into the canal of the premolar. Direct pulp capping. Anaesthesia: 2% lidocaine with 1:100,000 epinephrine	Liner of resin-modified glass ionomer cement (RMGIC) over biodentine and composite restoration. Biodentine. Growth factors, cytokines and microenvironments used to allow the regeneration process.
Mittal et al. 2021 (51)	Patients: no mention of the total number. Age: 16-34 yo Teeth: 36 necrotic uniraducular teeth divided into 4 groups (4 teeth/group). Pathology: necrosis with apical periodontitis Aetiology: N/A	4 groups: I: periapical bleeding II: Platelet rich fibrin (PRF) III: collagen IV: hydroxyapatite Double antibiotic paste (DAP) (metronidazole + ciprofloxacine). Collagen group: sterile granule of synthetic collagen. Hydroxyapatite group. Anaesthesia: - 1st visit: N/A - 2nd visit: 3% mepivacaine no vasoconstrictor	Biodentine. GIC and composite restoration first appointment; then PRF.

Aguilar et al. 2021 (52)	Patients: 1 Age: 16 yo Teeth: 11 Pathology: necrosis with symptomatic apical periodontitis Aetiology: trauma	Overinstrumentation. $Ca(OH)_2$ and zinc oxide eugenol (ZOE). Collagen sponge over blood clot. Anaesthesia: 2% lidocaine with 1:100,000 epinephrine	White MTA. GIC (type II).
Lu et al. 2023 (37)	Patients: 29 (20 F + 17 M) Age: average 20.5 yo Teeth: 37 teeth Pathology: necrosis with or without apical periodontitis Aetiology: 10 due to caries and 27 due to trauma	Overinstrumentation. Resorbable CollaCote placed over the blood clot, followed by the placement of a 2-mm thickness of iRoot BP plug. Anaesthesia: 3% carbocaine no vasoconstrictor	CaOH paste. GIC for 2 weeks.
Al-Rawhani et al. 2024 (7)	Patients: 31 patients Age: 10-35 yo Teeth: 2 groups of uniradicular teeth. Pathology: necrosis and apical periodontitis Biodentine vs MTA. *Biodentine group*: 13 maxillary central incisors, 4	Biodentine vs MTA. Overinstrumentation. Collagene sponge over blood clot. Anaesthesia: - 1st visit: 4% articaine with 1:200,000 epinephrine - 2nd visit: 3% mepivacaine no vasoconstrictor	CaOH first appointment. MTA (controlled group) vs Biodentine (intervention).

	maxillary lateral incisors, 1 mandibular central incisor. Aetiology: 14 teeth due to trauma; 4 due to caries. *MTA group*: 10 maxillary central incisors, 5 maxillary lateral incisors and 3 mandibular central incisors. Aetiology: 15 due to trauma, 3 due to caries.		
Brizuela et al. 2024 (53)	Patients: 2 cases Age: 50 yo M and 43 yo M Teeth: tooth 35 and tooth 21 Pathology: necrosis and apical periodontitis Ethiology: caries	Umbelical-cord derived MSCs (UC-MSCs) encapsulated in PPP (platelet poor plasma) matrix. Anaesthesia: - 1st visit: 2% lidocaine with 1:100,000 epinephrine - 2nd visit: 3% mepivacaine no vasoconstrictor	Biodentine.

The duration of the follow ups and the results of each article are described in [Table 3].

Table 3. Follow-up period and results.

	Follow up and tests	**Results**
Saoud et al. 2016 (41)	8-26 months follow ups. Pulp tests and periapicals.	Criteria: healed, healing, disease. Healed: 2 teeth Healing: 5 teeth
Nagas et al. 2018 (42)	1 months follow up and then every 6 months. 60 months. Pulp tests (cold and electric) and periapicals.	Teeth asymptomatic and healed. Total resolution of apical radiolucency and restoration of periradicular tissues.
Samra et al. 2018 (43)	3, 6, 9 months. Pulp tests and periapicals.	Healed teeth with absence of signs and symptoms. Case 1: at 3 months slight decreased periapical lesion. At 6 and 9 months even more decreased. 30 months after, complete healing. Asymptomatic. No responses to pulp tests. Case 2: asymptomatic and functional tooth. No response to pulp tests. Case 3: same as case 1.
Nageh et al. 2018 (44)	3, 6, 9 and 12 months. Electric pulp test and periapicals.	Highly significant difference between baseline and 12-months-follow up period. All teeth healed after 12 months.
Jha et al. 2019 (45)	6, 12, 18 months. Pulp tests (cold and electric) and periapicals.	Criteria: healed, healing, disease. 13/15 completely healed at 18-month follow-up in the SealBio group. 12/15 completely healed at the 18th month in the obturation group. No significant difference between the 2 groups.

Arslan et al 2019 (46)	Up to 12 months. Electric pulp test and periapicals.	Vitality (positive or negative) for REP. 46 teeth successfully passed the results (20 non-surgical and 26 rep). 2/26 fail in REP vs 4/20 fail in CRCT-treated cases.
Meza G et al 2019 (47)	36 months. Pulp tests (cold and electric) and periapicals and CBCT.	Healed tooth. The patient stayed asymptomatic during the whole follow-up period. Last examination (3 years after treatment): delayed response to cold test. Electric pulp test was positive. Blood perfusion test was mildly positive.
El-Kateb et al 2020 (48)	1, 3-, 6-, 9- and 12-months of clinic and radiographic control. 3, 6 and 12 months of MRI assessment.	Healing teeth at 3 months. Healed teeth at 12 months. Asymptomatic teeth during follow-up period.
Brizuela et al. 2020 (49)	6 and 12 months. 5 years. Pulp tests (cold, hot and electric) and periapicals and CBCT.	1 patient with pain with percussion test in the REP group. At 12 months, both groups showed negative responses in tests. Sensitivity tests results at 12 months: increase of pulp response higher in the REP group than in RCT group. Significant reduction in anteroposterior dimension of lesions between the 6th and 12th month in the REP group rather than in RCT. In REP, vitality has improved during time.
Feitosa et al 2021 (50)	3; 6; 9 and 12 months. Electric pulp test and periapicals and CBCT	At 3- and 6-months positive results were registered. At 3 months all the patients showed light discomfort in the periapical zone, lasting for those first 2-3 months. At 6 months: tomographic images show reduction in periapical radiolucency. Electric pulp tests showed a positive response with similar values to patient's healthy teeth.

		1 year: complete regression of periapical lesion for 2 patients; almost complete for a third patient.
Mittal et al 2021 (51)	3, 6, 9, 12 months. Pulp tests (cold, hot and electric) and periapicals.	Asymptomatic patients during the whole follow-up period. Improvement of periapical and apical conditions. 1-3 months: no significant difference between groups. 3-6 months: PRF group = 22.3% positive response; collagen group = 11.1%; hydroxyapatite and periapical bleeding show no response up to this time. 9 months: PRF gr 44.4% vs 33.3% of collagen gr; hydroxyapatite = 22.2%. Periapical bleeding = no response. 12 months: PRF 66.6%; collagen = 44.4%; hydroxyapatite = 33.3%; periapical bleeding = 11.1%.
Aguilar et al. 2021 (52)	6, 13, 17 months. Pulp test (cold) and percussion test and periapicals.	Asymptomatic in every control. Healed periodontium.
Lu et al. 2023 (37)	3, 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96 months. Clinical (pain/discomfort, crown discoloration, swelling, sinus tract, mobility, pulp sensibility, root resorption) and radiographic control: CBCT in the last follow-up if patient consented.	The overall success rate was 89.2% (33/37). 4 teeth were classified as failure. 35.1% of teeth regained pulp sensibility, and 40.5% of the teeth exhibited intracanal calcification.
Al-Rawhani et al 2024 (7)	6, 9, 12 and 18 months.	No significant difference between the two groups.

	Pulp tests (cold and electric) and periapicals.	After 18 months: 21/31 patients healed; 10/31 in process of healing. No failure cases.
Brizuela et al. 2024 (53)	1, 6, 12 months and 5 years. Pulp tests (cold and electric) and periapicals and CBCT.	Asymptomatic patients throughout the whole follow-up period. First case: complete healing of apical lesion maintained over 5 years follow-up. Second case: progressive healing during the first year, reaching a complete healing at 5 years.

5. DISCUSSION

This study aims to identify if RETs are an available option to use in case of mature teeth with irreversible pulpitis or necrosis according to the literature. It is currently well consolidated that RETs are widely accepted as treatment for immature teeth (33,34,54,55), but studies are investigating the possibility of implementing these techniques on mature teeth as well.
Since 1961 due to Nygaard Östby's pioneering work, RETs have continually evolved, with ongoing studies refining the techniques and materials used (18).

To investigate the objective of this study, 15 articles have been analyzed. The most scientifically relevant studies were randomized control trials by Jha et al. 2019, El-Kateb et al. 2020, Brizuela et al. 2020 and Mittal et al. 2021, followed by the randomized control studies of Arslan et al. 2019, Feitosa et al. 2021 and Al-Rawhani et al. 2024. The findings of these articles were supplemented by two retrospective studies by Meza et al. 2019 and Lu et al. 2023, the case series by Saoud et al. 2016 and Samra et al. 2018 and the clinical cases by Nagas et al. 2018, Nageh et al. 2018, Aguilar et al. 2021.
The lowest level of evidence was provided by the case report by Brizuela et al. 2024.

According to the results of this review, RETs in mature permanent teeth are well accepted as alternative to the gold standard RCT; that said, the findings should be taken with caution as not all the studies are randomized controlled clinical trials, including clinical cases as well. Moreover, all the studies considered mentioned that more studies were necessary to be able to confirm with certainty the effectiveness of the newer techniques (7,37,41–53).

5.1. Patient age

The age of the patients in the articles varies widely. The youngest being 8 years old (41,45) and the oldest 58 years old (49), with the average age being of 25 (26,2).
This age variability could lead to different outcomes, especially due to the anatomical differences and changes in cells efficiency that occur with age. In fact, younger teeth tend to have wider root canals that allow the blood to flow into the canal more easily and promote angiogenesis (42). According to the article by Van Zant G and Liang Y 2003 stem cells have weaker functional abilities (self-renewal potential, development potential and interaction with

extrinsic signals) when aging (56). This suggests that the regenerative treatment outcome could change according to the patient's age.

It has been demonstrated that BMSCs have a lower capacity than PLSCs to regenerate a pulpal volume that is highly innervated and vascularized, and this ability decreases more with the donor's age (47,57,58). Moreover, older teeth present a thickening of the apical cementum and deviation of the apical foramina that could affect the stem cells ability to easily migrating into the canal (48).

This aspect warrants further investigation for two main reasons. First, there are not enough studies on the effects of aging over stem cells and tissues physiological functions (56). Second, positive results have been obtained for both young (7,37,42,43,48–51) and adult patients (7,44,46–51,53).

Chrepa et al. 2015 suggested that the concentration of MSC markers in a donor, rather than age, may be a more significant factor influencing regenerative outcomes. Moreover, some studies demonstrated that age was a non-significant factor. For example, Arslan et al. 2019 analysed age as "confounding variable" (together with sex, tooth number, master file, irrigation protocol, medicament type, time interval of intracanal medicament and intrapatient clustering), concluding that it had no significant relevance on the healing size of the radiographic lesion image ($P > 0.05$). Similarly, Al-Rawhani et al. 2024 found no significant difference between the two groups considering their characteristics, stating their agreement with the study of Arlsan et al. 2019.

While subgroup analysis based on age was not performed in their study, as age group stratification had not been done for many groups, Li et al. 2024 also mentioned different reviews supporting the concept that age doesn't have an influence on the treatment outcome (6,39,59–61). It is necessary to mention that the main aim of these cited studies was not to compare treatment outcomes to patients' age.

While the role of age in treatment outcomes remains uncertain, it seems that there is more consensus that sex is not an element that could have influence (48,62), with many articles even stated that their inclusion criteria did not include sex predilection (44,46,48,50,51).

5.2. Tooth type: uniradicular or multiradicular.

Only 3 articles (37,41,45) out of 15 include multiradicular teeth in their analysis.

In Saoud et al. 2016, 2 teeth were completely healed after the last follow-up, while 5 were still healing. Of these 5, 4 were molars (multirooted teeth). It is possible that molars require more

time to heal completely, but the periapical radiography of the following months would be necessary to identify the outcome.

Jha et al. 2019 suggested that uniradicular teeth with apical periodontitis were more likely to heal compared to multiradicular teeth, thus introducing bias into the study. For this reason, the number of single-rooted and multi-rooted teeth was balanced. There is no mention of any difference in the results given by uniradicular or multiradicular teeth.

Lu et al. 2021 found a different result: although the general outcome is favorable (89.2% teeth healed), 4 teeth failed. Among these 4 teeth, the mesial root of one lower molar showed a re-infection after its long-term follow up, leading to the recurrence of periapical radiolucency (PARL).

This may be due to bacteria microleakage and the only partial elimination of bacteria, that allowed the multiplication of microorganism and the failure of the case (37).

More studies on multiradicular cases are necessary to better understand the efficacy of RETs on these types of teeth.

5.3. Pathology and aetiology

All the studies of this review (7,37,41–46,48–53) analysed necrotic teeth, except for Meza et al. 2019 that described the case of a lower premolar with irreversible pulpitis. Therefore, there are not enough cases of irreversible pulpitis to make a comparison with necrotic teeth to be able to study whether RETs have a better prognosis in irreversible pulpitis or necrosis.

An analysis can be done on the aetiology: trauma or caries. RETs showed failure in two teeth of the study by Arslan et al. 2019, where one central incisor and one lateral necrotic incisor due to caries did not show a positive outcome. The author (46) suggests that it may be due to the lack of complete microbial and pulpal tissue cleaning.

Especially relevant is the study by Lu et al. 2023. Three cases of RETs resulted in failure: a maxillary left central incisor with trauma, presenting a periapical lesion because of reinfection, showed a larger infection in the control of 44 months, after an initial resolution; similarly, a central incisor with trauma showed a bigger image at 6 months follow-up; finally, a case of avulsion - and root resorption as consequence - of a maxillary right central incisor, showed external root resorption at 40 months with normal periapical image.

According to his study (37), the aetiology (caries or trauma) does not have an influence on the RETs outcome in mature necrotic teeth, while it does have it in immature necrotic teeth. Indeed, dental trauma negatively affects the Hertwig Epithelial Root Sheet (HERS) and the apical papilla, increasing the risk of RETs failure (37,63).

In Lu et al. 2023's suggestions, the actual cause of failure is the microleakage of bacteria that cause a reinfection of the canal; with no particular importance to the initial reason of the necrosis. This statement is in accordance with the study mentioned above by Arslan et al. 2019. Another interesting result found by Lu et al. 2023 is the comparison of failures between RCT and RETs.

The first data that was analysed and that gave an influence on the outcome was the previous presence of PARL. It had not significant relevance on RETs success rate, while it seemed to increase the risk of reinfection in the cases of traditional RCTs (37). This data was also confirmed in other articles of the literature (64,65). Moreover, RETs may facilitate the periapical lesions' resolution, creating a favourable microenvironment for tissue regeneration and repair (37,66,67).

A significant difference with RCT is the antimicrobial clearance and the bleeding induction during RETs. The derivative components allow to stimulate the innate and adaptive immune system, contributing to the healing and the vitality recovery that RCT cannot give (37).

5.4. Intracanal antibiotics and irrigants

It is understood that one of the most important elements to achieve success in treatments is to keep an environment as sterile as possible. Intracanal antibiotics are always used to control bacteria growth (18).

The type of antibiotics used during the techniques changed through the years: it was very common to use a triple antibiotic paste formed by ciprofloxacin, metronidazole and clindamycin (42–46), however more recent studies substituted it with a solution of two antibiotics, such as 2 mL penicillin/streptomycin and 250 mL 80 mg/mL gentamicin (47) or a double antibiotic paste (DAP) formed by metronidazole and ciprofloxacin (52).

Aside from the action of intracanal antibiotics, a seal between the coronal part of the root canals and the new restoration is essential to the treatment success (41,68).

To clean the root canal space, highly concentrated irrigants have been used which have not changed significantly through the years: sodium hypochlorite (NaOCl) is the main irrigation solution with a concentration between 1.5% (7,37,43,44,47,48,51) and 2.5% (41,46,52,53). These low concentrations are used to ensure effective disinfection while maintaining stem cell viability and preserving dentine growth factors (7).

NaOCl is used throughout the treatment, while EDTA is used in the final irrigation protocol after NaOCl to remove as much as possible the inorganic residues formed during the instrumentation.

It has been demonstrated that EDTA increases the survival ability and the manifestation of the stem cells in the apical papilla, contributing to the success of RETs (33). Moreover, according to some studies, in particular the study by Galler et al. 2016, DPSC's migration, differentiation and adhesion are indorsed by EDTA (69).

5.5. Overinstrumentation

All fifteen studies reported overinstrumentation to induce bleeding inside the canal. This result and the fact that many other studies in the literature have used and studied overinstrumentation, also compared to other types of scaffolds, makes it to be the gold standard for regenerative techniques (7,70). When compared to PRP and PRF, studies have shown that they are equal or inferior to bleeding induction as scaffold (7,27,28).

5.6. Anaesthesia

In RCTs, as in all dental procedures, relieving the patient's pain is one of the main goals. To achieve this, local anaesthesia is administered through either an infiltrative technique or the inferior alveolar nerve (IAN) block technique. The anaesthetic solutions used can be various, depending also on the patient's case, but commonly the most used are lidocaine and articaine. These solutions, usually, contain relatively high concentrations of vasoconstrictor, such as 1:2500 phenylephrine or 1:100,000 adrenaline (71).

The protocol for RETs, however, seems to be different, not so much in the type of anaesthetic solution, but in the concentration of vasoconstrictor.

In fact, only Saoud et al. 2016, Nagas et al. 2018, Nageh et al. 2018 and Feitosa et al. 2021 used 2% lidocaine with 1:100,000 epinephrine in their treatments, while other articles (48,52,53) that used this solution, reported it only for the first visit. Instead, a solution without vasoconstrictor was used when overinstrumentation was performed during the following appointment (48,52,53).

4% articaine with 1:200,000 epinephrine was used exclusively by Arslan et al. 2019 in the RCT group, while the RET group received 3% isocaine without vasoconstrictor. Similarly, Al-Rawhani et al. 2024 used articaine in the first appointment, whereas the anaesthetic option was 3% mepivacaine without vasoconstrictor during the second appointment, where apical bleeding was induced.

Another author that did not choose an anaesthetic solution with a vasoconstrictor was Lu et al. 2023. The election was 3% carbocaine.

3% mepivacaine without vasoconstrictor was the type of anaesthetic solution that was most used among the authors of this review, with seven studies out of fifteen (7,43,45,47,48,51,53) that chose it.

In terms of vasoconstrictor use, it can be noted that nine out of fifteen articles (7,37,43,45–48,51,53) used anaesthesia without vasoconstrictor.

One author, Brizuela et al. 2020, did not mention the type of anaesthesia used.

This preference for anaesthetics without vasoconstrictor might find an explanation in the finding that vasoconstrictors reduce the pulp blood flow (72,73), which is an unwanted effect during RETs. It is important that all the cells involved in the tissue regenerative process can easily enter the root canal. One way to facilitate a correct blood flow is the use of 3% mepivacaine without vasoconstrictor, followed by an intentional overinstrumentation. This advantage does not change the efficacy of the anaesthesia, especially if compared to lidocaine 2% with 1:100,000 epinephrine (72,74,75).

However, the case described by Samra et al. 2018 highlighted difficulties in inducing bleeding inside the canal. Various attempts were needed to achieve satisfactory blood flow, despite 3% mepivacaine without vasoconstrictor was used.

More studies comparing the type of anaesthesia and vasoconstrictor used and the outcome of RETs are needed to define whether the anaesthetic solution could be an influencing factor in the success of the regenerative treatments.

5.7. MTA vs Biodentine

The most used temporary cement is CaOH, which is placed as intracanal medication due to its characteristics: it is biocompatible, it has an alkaline pH (12.5-12.8) that makes it strongly antibacterial and it also has an influence on the periodontal recovery (76). Its advantages extend to RETs, as it has been shown to induce a release bioactive growth factors from dentin, encouraging SCAP proliferation (7,34).

Two materials are the choices of election as coronal barrier: MTA and Biodentine.

Examining the articles, it seems that MTA was the material of choice at first (41–44,46), then Jha et al. in 2019 compared it to another material – SealBio – to study a new technique that could provide a good biological seal compared to the traditional obturating techniques (45), finding a positive result in favour of the novel material.

In recent years, Biodentine seemed to be the material of choice to seal the canal (47–51,53). That said, other studies continued to explore other materials, such as Lu et al. in 2023 that tried

iRoot BP plug - a bioceramic putty that is very similar to MTA in its characteristics, except for the setting time which is shorter (77).

Al-Rawhani et al. (7) compared the two main materials using MTA for the control group and Biodentine in the intervention group.

The advantages of MTA are its biocompatibility, sealing and margin adaptability (78), promotion and releasing of molecules that are crucial in the formation of new tissue in the pulp space, osteoblastic feasibility, proliferation and differentiation thanks to calcium ions, and antimicrobial effect due to the alkalinity formed by hydroxide ions (7,79). Moreover, it has an impact on the angiogenic process, modifying the vascular endothelial growth factor (VEGF) (7).

Biodentine is very similar to MTA in these characteristics, but Al-Rawhani et al. 2024, as other authors, found that it can also increase the production of hard tissue bridges and the production of anti-inflammatory cytokines while defeating pro-inflammatory cytokines (7,80).

One of the reasons why MTA was substituted by Biodentine is that it might lead to tooth discoloration, causing an aesthetic problem (81). This disadvantage was solved by a new white MTA, which was used by Nageh et al. 2018 and by Aguilar et at. 2021. They reconfirmed that MTA rapidly induced SCAP migration and enhanced their proliferation (52).

Both materials satisfy the necessities for treatment success.

5.8. Scaffolds and cells used

The potential stem cells available for RETs usually comes from the apical papilla present in the open apex of immature teeth. As mature teeth do not have the apical papilla, the alternative is to take them either locally from the periodontal ligament (PLSCs) or from the bone marrow (BMSCs) (38). Many studies used the bleeding induction technique to fill the apical part of the canal with blood containing cells that act in the regeneration process, providing a well-organised scaffold and supplying the necessary growth factors (7,47).

The PRF technique used by Nageh et al. 2018 showed positive radiological results at 12 months with a complete healing of the periapical lesion. Beyond the release of cytokines, promotion of stem cell activity and angiogenesis, the advantage found by authors like Nageh et al. 2018, Meza et al. 2019 or Al-Rawhani et al. 2024 in using PRF instead of using directly PRP is the elimination of the need for an anticoagulant, since it resembles natural blood.

Meza et al. 2019 used PRF taken from the patients' blood (specifically they used leukocyte PRF), obtaining positive results in their conclusions. Once again, one of the main advantages seemed to be that this graft doesn't require any anticoagulant as it is completely autologous, simplifying the technique.

Mittal et al. 2021 analysed four different methods and found out that the best results were given when PRF was used. The comparison was done with collagen, periapical bleeding and hydroxyapatite. The radiological results improved after every control, passing from 22.3% at 3 and 6 months, to 44.4% at the ninth month and 66.6% at the last visit (12 months) (51).

Although there are many studies showing the positive results of PRF, it has not conclusively been proven to be more effective than a simple blood clot (7,62,82).

Provoked bleeding induces the migration of MSCs, but there are many uncontrollable variables that could lead to inconclusive results. This is why Brizuela et al. 2024 attempted to have more control by the transplantation of allogenic UC-MSCs, obtaining positive results even in the long-span follow-up period of five years.

5.9. Follow up and results

Considering the number of patients included in the studies, the positive results of Jha et al. 2019, where at 18 months follow-up 86.6% (13/15) was completely healed and 14.4% was healing, can be compared to studies like the one by Arslan et al. 2019 that found 46 teeth out of 56 successfully passed the tests at 12 months. Similarly, Brizuela et al. 2020 found an increase in the positive results (from 6% to 56% in cold test, 0% to 28% in hot test and 17% to 50% in electrical test) at 12 months follow-up. Mittal et al. 2021 obtained a 66.6% success at 12 months follow-up, while Lu et al. 2023 found 89.2% of success (33/37 teeth). Al-Rawhani et al. 2024 reports that 21/31 patients healed after 18 months.

All these results demonstrate the initial hypothesis of the success of RETs in mature teeth with irreversible pulpitis or necrosis.

Every article used pulp tests such as a cold test and/or electric pulp test to record the tooth's response. Every study used periapical x-rays during checks-up, but five articles (37,47,49,50,53) also used a CBCT to register more precise results: Meza et al. 2019 took a CBCT at 36-months follow-up period with intact periapical bone structures and formation of dentine bridge in the middle third of the root and calcification of the canal in the apical third; Brizuela et al. 2020 scored a decrease in the lesion dimension value of 0.9 mm - from 2.7 mm at 6 months to 1.8 at 12 months - (results compared to RCT group, where the difference was of 0.9 mm too, but the values ranged from 2.4 mm to 1.5 mm). A different result was found by Feitosa et al. 2021 because the computed tomography showed that one year was not sufficient to have the complete recuperation of the periapical lesion, although all teeth showed a positive response to electrical pulp test.

Promising results were obtained by also Lu et al. 2023 which measured the level of the periapical lesion following the periapical index (PAI): starting from a PAI of 4 or 5, 32 teeth scored a PAI of 1 (healthy periapical area) and just 1 tooth scored a PAI of 2; while 14 teeth didn't change and 1 tooth failed due to external root resorption. Among the different intervals, a noteworthy difference was found only in PAI scores between the 3–6 month and 7–12-month intervals ($p = .039$). No significant differences between intervals longer than 12 months were observed ($p > .05$) (37). Brizuela et al. 2024 also used CBCT to record PAI index for the described 2 cases, where PAI was maintained to 0 for 5 years (from the first year follow-up to the fifth) in the first case, while the score improved significantly from the first year to the fifth in the case of the second patient, because its PAI passed from being 3 in the 1-year follow up, to be of 0. In this case, the healing process of the periapical area took more time than in the previous cases.

5.10. Limitations and future directions

Some aspects that could impact the analysis of this study are related to the different samples that each article has, different teeth studied, materials used and follow-up duration. This diversity has enriched the comparison between studies, but it also made a direct comparison more complex.

Standardizing of controlled variables in RETs should be considered for futures studies to facilitate consistency in outcome reporting, reduce heterogeneity and improve reliability.

Another limitation comes from the fact that it is not possible to biologically analyse the nature of the tissue formed in the pulp canal after the treatment due to the ethical and clinical aspects. As such, the results are only based on generic tests like vitality tests and radiographic tests. That said, there are some articles in the literature that could confirm the development of an innate immune system within the root canal, namely the study by Arslan et al. 2019.

In future, high-quality clinical trials with larger sample size are required to determine the success of RETs in non-vital permanent teeth. A recommended methodology would be the one used by Arslan et al. 2019, that compared RCT to RETs, conducting immunological studies to assess the treatment outcome. Future clinical directions should include extended monitoring and follow-up.

Involving more multiradicular teeth in the analysis to compare with uniradicular teeth could provide more detailed insights into the efficacy of RETs across different types of teeth. Moreover, extending studies on chronic necrosis with apical periodontitis and fistulisation would offer valuable additional data.

Regarding patients' medical history, the articles of this review did not consider patients with systematic pathologies, with some articles explicitly listed medical conditions as exclusion criterion (37,43–46,51). Perhaps, future research on RETs could potentially explore outcomes in this patient group as well.

Finally, future research should aim to standardize outcome measures in RETs to have better consistency in outcome reporting, minimize variability and enhance the reliability and overall quality of evidence in this field.

6. CONCLUSION

After reviewing the recollected data of this study about RETs in mature permanent teeth with irreversible pulpitis or necrosis, it can be concluded that:

- While RETs show good outcomes in the first few years following treatment, there is not enough scientific evidence that validates the success rate in longer follow-up periods (>5 years). Additional studies with extended follow-up are needed to better analyse the long-term survival of teeth treated with RETs.
- RETs are still novel procedures in mature teeth, but the results suggest that they may become a viable and reliable alternative to RCTs.
- Effective bacterial elimination and adequate coronal sealing are essential factors in the success of RETs.
- Patients' age may be an influencing factor on RET's success, while sex does not appear to have an influence.
- Further studies on multiradicular teeth are needed to determine whether RETs' success varies depending on the type of tooth treated.
- Contrary to immature teeth, the aetiology of irreversible pulpitis or necrosis in mature teeth does not seem to affect RETs' outcome.

7. SUSTAINABILITY

RETs in mature teeth appear support a more sustainable dental practice. By preserving the natural tooth, avoiding the need of more invasive treatments, the consequence is a reduction in biological waste and prosthetics' recurrence; saving time, money and energy (83).

One significant problem in dentistry about environmental pollution is the occurrence of patients' appointments, that increases travel-related CO2 emissions. RETs could reduce the

need for further re-treatments, thereby decreasing the number of visits, lowering the environmental impact (84).

Regarding material waste, RETs primarily use autologous materials, creating a natural “reuse” cycle, more sustainable than synthetic or natural materials, like gutta-percha, often not biodegradable. Their use increases the environmental waste, pollution, and energy consumption during fabrication (85). Indeed, traditional RCTs typically use higher environmental footprint materials compared to RETs.

According to Duane et al. 2020, 4.9 kg of carbon dioxide equivalent (CO2 eq) emissions come from a RCT procedure: an equivalent of a 30 km car drive. This result comes from dental clothing, surface disinfection, disposable apron (paper and/or plastic), single-use stainless steel instrument and the electricity used.

The journey to reduce to minimum the pollution produced is still long, but RETs are a way to improve the environmental impact (86).

8. REFERENCES

1. Ghannam MG, Alameddine H, Bordoni B. Anatomy, Head and Neck, Pulp (Tooth). En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citado 1 de noviembre de 2024]. Disponible en: http://www.ncbi.nlm.nih.gov/books/NBK537112/

2. Meng H, Hu L, Zhou Y, Ge Z, Wang H, Wu C tse, et al. A Sandwich Structure of Human Dental Pulp Stem Cell Sheet, Treated Dentin Matrix, and Matrigel for Tooth Root Regeneration. Stem Cells Dev. 15 de abril de 2020;29(8):521-32. doi: 10.1089/scd.2019.0162. https://pubmed.ncbi.nlm.nih.gov/32089088/

3. Dabuleanu M. Pulpitis (reversible/irreversible). J Can Dent Assoc. 2013;79:d90. https://pubmed.ncbi.nlm.nih.gov/24059490/

4. Donnermeyer D, Dammaschke T, Lipski M, Schäfer E. Effectiveness of diagnosing pulpitis: A systematic review. Int Endod J. octubre de 2023;56(S3):296-325. doi: 10.1111/iej.13762. doi: 10.1111/iej.13762.

5. Patel S, Chong BS. Chapter 3 - Diagnosis. En: Chong BS, editor. Harty’s Endodontics in Clinical Practice (Sixth Edition) [Internet]. Churchill Livingstone; 2010. p. 17-33. Disponible en: https://www.sciencedirect.com/science/article/pii/B9780702031564000061

6. Asgary S, Eghbal MJ. Challenging the Misnomer of Irreversible Pulpitis and Deliberating the Urgent Need for Reclassification of Pulpal Diseases Based on the Efficacy of Vital Pulp Therapies: An Overview of Systematic Reviews. Iran Endod J. 25 de septiembre de 2023;18(4):202-5. doi: 10.22037/iej.v18i4.43035. https://pubmed.ncbi.nlm.nih.gov/37829832/

7. Al-rawhani AH. Regenerative Treatment of Mature Teeth with Pulp Necrosis and Apical Periodontitis Using Biodentine Compared with MTA: Randomized Controlled Clinical Trial. Eur Endod J [Internet]. 2024 [citado 3 de noviembre de 2024]; Disponible en: https://eurendodj.com/jvi.aspx?un=EEJ-30075&volume=

8. Berman LH, Hartwell GR. Diagnosis. En: Cohen's Pathways of the Pulp [Internet]. Elsevier; 2011 [citado 3 de noviembre de 2024]. p. 2-39. Disponible en: https://linkinghub.elsevier.com/retrieve/pii/B9780323064897000011

9. Al-Afifi NA, Al-Amery SM. THE KEYS TO A SUCCESSFUL ROOT CANAL TREATMENT. Electron J Univ Aden Basic Appl Sci. 3 de enero de 2024;4(4):377-83. doi: 10.47372/ejua-ba.2023.4.306

10. Wei X, Yang M, Yue L, Huang D, Zhou X, Wang X, et al. Expert consensus on regenerative endodontic procedures. Int J Oral Sci. diciembre de 2022;14(1):55. doi: 10.1038/s41368-022-00206-z. https://pubmed.ncbi.nlm.nih.gov/36450715/

11. Vías de la pulpa. 10ª ed. Barcelona [etc.]: Elsevier Science; 2011. Available from: https://books.google.it/books/about/Cohen_Vías_de_la_Pulpa_10_ed_+_Student.html?id=6DKUoWfGonQC&redir_esc=y

12. Ganjo Ghawtha Khudhur, Diyar Khalid Bakr. Human dental pulp stem cells differentiation into odontoblast and osteoblast-likecells on scaffolds contain bioactive materials. Cell Mol Biol. 5 de junio de 2024;70(6):135-41. doi: 10.14715/cmb/2024.70.6.21. https://pubmed.ncbi.nlm.nih.gov/38836669/

13. Zhao X, Li Q, Guo Z, Li Z. Constructing a cell microenvironment with biomaterial scaffolds for stem cell therapy. Stem Cell Res Ther. 22 de noviembre de 2021;12(1):583. doi: 10.1186/s13287-021-02650-w. https://pubmed.ncbi.nlm.nih.gov/34809719/

14. Ahmed GM, Abouauf EA, AbuBakr N, Fouad AM, Dörfer CE, Fawzy El-Sayed KM. Cell-Based Transplantation versus Cell Homing Approaches for Pulp-Dentin Complex

Regeneration. Stem Cells Int. 2021;2021(1):8483668. doi: 10.1155/2021/8483668. https://pubmed.ncbi.nlm.nih.gov/34646323/

15. Li XL, Fan W, Fan B. Dental pulp regeneration strategies: A review of status quo and recent advances. Bioact Mater. 1 de agosto de 2024;38:258-75. doi: 10.1016/j.bioactmat.2024.04.031. https://pubmed.ncbi.nlm.nih.gov/38745589/

16. Torabinejad M, Turman M. Revitalization of Tooth with Necrotic Pulp and Open Apex by Using Platelet-rich Plasma: A Case Report. J Endod. febrero de 2011;37(2):265-8. doi: 10.1016/j.joen.2010.11.004. https://pubmed.ncbi.nlm.nih.gov/21238815/

17. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, et al. SHED: Stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci U S A. 25 de abril de 2003;100(10):5807. doi: 10.1073/pnas.0937635100. https://pubmed.ncbi.nlm.nih.gov/12716973/

18. Östby BN. The Role of the Blood Clot in Endodontic Therapy an Experimental Histologic Study. Acta Odontol Scand. 1 de enero de 1961;19(3-4):323-53. https://pubmed.ncbi.nlm.nih.gov/14482575/

19. American Association of Endodontists. J Am Dent Assoc. agosto de 1977;95(2):272-4.

20. Iwaya S ichi, Ikawa M, Kubota M. Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. Dent Traumatol. 2001;17(4):185-7. doi: 10.1034/j.1600-9657.2001.017004185.x. https://pubmed.ncbi.nlm.nih.gov/11585146/

21. Huang GTJ, Sonoyama W, Liu Y, Liu H, Wang S, Shi S. The Hidden Treasure in Apical Papilla: The Potential Role in Pulp/Dentin Regeneration and BioRoot Engineering. J Endod. junio de 2008;34(6):645-51. doi: 10.1016/j.joen.2008.03.001. https://pubmed.ncbi.nlm.nih.gov/18498881/

22. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci U S A. 21 de noviembre de 2000;97(25):13625. doi: 10.1073/pnas.240309797. https://pubmed.ncbi.nlm.nih.gov/11087820/

23. Andreasen JO, Farik B, Munksgaard EC. Long-term calcium hydroxide as a root canal dressing may increase risk of root fracture. Dent Traumatol. 2002;18(3):134-7. doi: 10.1034/j.1600-9657.2002.00097.x. https://pubmed.ncbi.nlm.nih.gov/12110105/

24. Hachmeister D, Schindler W, Walkeriii W, Deneethomas D. The Sealing Ability and Retention Characteristics of Mineral Trioxide Aggregate in a Model of Apexification. J Endod. mayo de 2002;28(5):386-90. doi: 10.1097/00004770-200205000-00010. https://pubmed.ncbi.nlm.nih.gov/12033201/

25. Hoshino E, Kurihara-Ando N, Sato I, Uematsu H, Sato M, Kota K, et al. In-vitro antibacterial susceptibility of bacteria taken from infected root dentine to a mixture of ciprofloxacin, metronidazole and minocycline. Int Endod J. 1996;29(2):125-30. doi: 10.1111/j.1365-2591.1996.tb01173.x. https://pubmed.ncbi.nlm.nih.gov/9206436/

26. Banchs F, Trope M. Revascularization of Immature Permanent Teeth With Apical Periodontitis: New Treatment Protocol? J Endod. abril de 2004;30(4):196-200.

27. Mooney DJ, Powell C, Piana J, Rutherford B. Engineering Dental Pulp-like Tissue in Vitro. Biotechnol Prog. 1996;12(6):865-8. doi: 10.1097/00004770-200404000-00003. https://pubmed.ncbi.nlm.nih.gov/15085044/

28. Ding RY, Cheung GS pan, Chen J, Yin XZ, Wang QQ, Zhang CF. Pulp Revascularization of Immature Teeth With Apical Periodontitis: A Clinical Study. J Endod. 1 de mayo de 2009;35(5):745-9. doi: 10.1016/j.joen.2009.02.009. https://pubmed.ncbi.nlm.nih.gov/19410097/

29. Hargreaves KM, Geisler T, Henry M, Wang Y. Regeneration Potential of the Young Permanent Tooth: What Does the Future Hold? J Endod. 1 de julio de 2008;34(7, Supplement):S51-6. doi: 10.1016/j.joen.2008.02.032. https://pubmed.ncbi.nlm.nih.gov/18565373/

30. Tatullo M, Spagnuolo G, Codispoti B, Zamparini F, Zhang A, Esposti MD, et al. PLA-Based Mineral-Doped Scaffolds Seeded with Human Periapical Cyst-Derived MSCs: A Promising Tool for Regenerative Healing in Dentistry. Materials. 16 de febrero de 2019;12(4):597. doi: 10.3390/ma12040597. https://pubmed.ncbi.nlm.nih.gov/30781537/

31. Guimarães BM, Tartari T, Marciano MA, Vivan RR, Mondeli RFL, Camilleri J, et al. Color Stability, Radiopacity, and Chemical Characteristics of White Mineral Trioxide Aggregate

Associated with 2 Different Vehicles in Contact with Blood. J Endod. junio de 2015;41(6):947-52. doi: 10.1016/j.joen.2015.02.008 https://pubmed.ncbi.nlm.nih.gov/25799532/

32. Digka A, Dds, Anna D, Sakka D, Lyroudia K. International Journal of Dentistry and Oral Health Regenerative procedures in mature teeth: a new era in endodontics? A systematic review. Int J Oral Health Dent. 1 de abril de 2020;6:1.

33. Glynis A, Foschi F, Kefalou I, Koletsi D, Tzanetakis GN. Regenerative Endodontic Procedures for the Treatment of Necrotic Mature Teeth with Apical Periodontitis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. J Endod. junio de 2021;47(6):873-82. doi: 10.1016/j.joen.2021.03.015. https://pubmed.ncbi.nlm.nih.gov/33811981/

34. Scelza P, Gonçalves F, Caldas I, Nunes F, Lourenço ES, Tavares S, et al. Prognosis of Regenerative Endodontic Procedures in Mature Teeth: A Systematic Review and Meta-Analysis of Clinical and Radiographic Parameters. Materials. 6 de agosto de 2021;14(16):4418. doi: 10.3390/ma14164418 https://pubmed.ncbi.nlm.nih.gov/34442940/

35. Aruede G, Pepper T. Anatomy, Permanent Dentition. En: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [citado 10 de noviembre de 2024]. Disponible en: http://www.ncbi.nlm.nih.gov/books/NBK570590/

36. Kim U, Kim S, Choi SM, Kang MK, Chang I, Kim E. Regenerative Endodontic Procedures with Minced Pulp Tissue Graft in Mature Permanent Teeth: A Clinical study. J Endod [Internet]. 12 de octubre de 2024 [citado 19 de octubre de 2024];0(0). Disponible en: https://www.jendodon.com/article/S0099-2399(24)00529-6/abstract

37. Lu J, Kahler B, Jiang X, Lu Z, Lu Y. Treatment outcomes of regenerative endodontic procedures in nonvital mature permanent teeth: a retrospective study. Clin Oral Investig. diciembre de 2023;27(12):7531-43. doi: 10.1007/s00784-023-05343-1. https://pubmed.ncbi.nlm.nih.gov/37875745/

38. Paryani K, Kim SG. Regenerative Endodontic Treatment of Permanent Teeth after Completion of Root Development: A Report of 2 Cases. J Endod. julio de 2013;39(7):929-34. doi: 10.1016/j.joen.2013.04.029 https://pubmed.ncbi.nlm.nih.gov/23791266/

39. Asgary S, Roghanizadeh L, Eghbal MJ, Akbarzadeh Baghban A. Managing failed vital pulp therapies in mature permanent teeth in a retrospective cohort study, with success and

survival rates of managing protocols. Sci Rep. 21 de mayo de 2024;14(1):11621. doi: 10.1038/s41598-024-62565-3. https://pubmed.ncbi.nlm.nih.gov/38773252/

40. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 29 de marzo de 2021;n71. doi: 10.1136/bmj.n71. https://pubmed.ncbi.nlm.nih.gov/33782057/

41. Saoud TM, Martin G, Chen YHM, Chen KL, Chen CA, Songtrakul K, et al. Treatment of Mature Permanent Teeth with Necrotic Pulps and Apical Periodontitis Using Regenerative Endodontic Procedures: A Case Series. J Endod. enero de 2016;42(1):57-65. doi: 10.1016/j.joen.2015.09.015. https://pubmed.ncbi.nlm.nih.gov/26525552/

42. Nagas E, Uyanik MO, Cehreli ZC. Revitalization of necrotic mature permanent incisors with apical periodontitis: a case report. Restor Dent Endod. 2018;43(3):e31. doi: 10.5395/rde.2018.43.e31. https://pubmed.ncbi.nlm.nih.gov/30135850/

43. Samra R, Elbackly R, Aly H, Nouh S, Moussa S. REVASCULARIZATION IN MATURE PERMANENT TEETH WITH NECROTIC PULP AND APICAL PERIODONTITIS: CASE SERIES. Alex Dent J. 1 de agosto de 2018;43:7-12. 10.21608/adjalexu.2018.57617

44. Nageh M, Ahmed GM, El-Baz AA. Assessment of Regaining Pulp Sensibility in Mature Necrotic Teeth Using a Modified Revascularization Technique with Platelet-rich Fibrin: A Clinical Study. J Endod. octubre de 2018;44(10):1526-33. doi: 10.1016/j.joen.2018.06.014. https://pubmed.ncbi.nlm.nih.gov/30174103/

45. Jha P, Virdi MS, Nain S. A Regenerative Approach for Root Canal Treatment of Mature Permanent Teeth: Comparative Evaluation with 18 Months Follow-up. Int J Clin Pediatr Dent. junio de 2019;12(3):182. doi: 10.5005/jp-journals-10005-1616. https://pubmed.ncbi.nlm.nih.gov/31708612/

46. Arslan H, Ahmed HMA, Şahin Y, Doğanay Yıldız E, Gündoğdu EC, Güven Y, et al. Regenerative Endodontic Procedures in Necrotic Mature Teeth with Periapical Radiolucencies: A Preliminary Randomized Clinical Study. J Endod. julio de 2019;45(7):863-72. doi: 10.1016/j.joen.2019.04.005. https://pubmed.ncbi.nlm.nih.gov/31155298/

47. Meza G, Urrejola D, Saint Jean N, Inostroza C, López V, Khoury M, et al. Personalized Cell Therapy for Pulpitis Using Autologous Dental Pulp Stem Cells and Leukocyte Platelet-rich

Fibrin: A Case Report. J Endod. febrero de 2019;45(2):144-9. doi: 10.1016/j.joen.2018.11.009. https://pubmed.ncbi.nlm.nih.gov/30711169/

48. El-Kateb NM, El-Backly RN, Amin WM, Abdalla AM. Quantitative Assessment of Intracanal Regenerated Tissues after Regenerative Endodontic Procedures in Mature Teeth Using Magnetic Resonance Imaging: A Randomized Controlled Clinical Trial. J Endod. 1 de mayo de 2020;46(5):563-74. doi: 10.1016/j.joen.2020.01.026. https://pubmed.ncbi.nlm.nih.gov/32173020/

49. Brizuela C, Meza G, Urrejola D, Quezada MA, Concha G, Ramírez V, et al. Cell-Based Regenerative Endodontics for Treatment of Periapical Lesions: A Randomized, Controlled Phase I/II Clinical Trial. J Dent Res. 1 de mayo de 2020;99(5):523-9. doi: 10.1177/0022034520913242. https://pubmed.ncbi.nlm.nih.gov/32202965/

50. Feitosa VP, Mota MNG, Vieira LV, de Paula DM, Gomes LLR, Solheiro LKR, et al. Dental Pulp Autotransplantation: A New Modality of Endodontic Regenerative Therapy—Follow-Up of 3 Clinical Cases. J Endod. 1 de septiembre de 2021;47(9):1402-8. doi: 10.1016/j.joen.2021.06.014. https://pubmed.ncbi.nlm.nih.gov/34175322/

51. Mittal N, Baranwal HC, Kumar P, Gupta S. Assessment of Pulp Sensibility in the Mature Necrotic Teeth using Regenerative Endodontic Therapy with Various Scaffolds – Randomised Clinical Trial. Indian J Dent Res. junio de 2021;32(2):216. Doi: 10.4103/ijdr.ijdr_253_21. https://pubmed.ncbi.nlm.nih.gov/34810392/

52. Aguilar R.B., Chaparro A.H., Tortolero DD. Procedimiento Endodóntico Regenerativo en Diente Maduro Permanente Traumatizado: Reporte de Caso [Internet]. [citado 30 de octubre de 2024]. Disponible en: https://www.canalabierto.cl/numero-43/procedimiento-endodontico-regenerativo-en-diente-maduro-permanente-traumatizado-reporte-de-caso

53. Brizuela C, Meza G, Khoury M. Revolutionizing Endodontics: Innovative Approaches for Treating Mature Teeth With Closed Apices and Apical Lesions: A Report of Two Cases. J Endod. 1 de mayo de 2024;50(5):596-601. DOI: 10.1016/j.joen.2024.02.012. https://pubmed.ncbi.nlm.nih.gov/38387795/

54. ElSheshtawy AS, Nazzal H, El Shahawy OI, El Baz AA, Ismail SM, Kang J, et al. The effect of platelet-rich plasma as a scaffold in regeneration/revitalization endodontics of immature permanent teeth assessed using 2-dimensional radiographs and cone beam computed

tomography: a randomized controlled trial. Int Endod J. julio de 2020;53(7):905-21. Doi: 10.1111/iej.13303. https://pubmed.ncbi.nlm.nih.gov/32249441/

55. Lei L, Chen Y, Zhou R, Huang X, Cai Z. Histologic and Immunohistochemical Findings of a Human Immature Permanent Tooth with Apical Periodontitis after Regenerative Endodontic Treatment. J Endod. 1 de julio de 2015;41(7):1172-9. Doi: 10.1016/j.joen.2015.03.012. https://pubmed.ncbi.nlm.nih.gov/25931029/

56. Zant GV, Liang Y. The role of stem cells in aging. Exp Hematol. 1 de agosto de 2003;31(8):659-72. DOi: 10.1016/S0301-472X(03)00088-2. https://pubmed.ncbi.nlm.nih.gov/12901970/

57. Peng L, Ye L, Zhou X dong. Mesenchymal Stem Cells and Tooth Engineering. Int J Oral Sci. marzo de 2009;1(1):6-12. Doi: 10.4248/ijos.08032. https://pubmed.ncbi.nlm.nih.gov/20690498/

58. Murakami M, Hayashi Y, Iohara K, Osako Y, Hirose Y, Nakashima M. Trophic Effects and Regenerative Potential of Mobilized Mesenchymal Stem Cells from Bone Marrow and Adipose Tissue as Alternative Cell Sources for Pulp/Dentin Regeneration. Cell Transplant. 1 de septiembre de 2015;24(9):1753-65. Doi: 10.3727/096368914X683502. https://pubmed.ncbi.nlm.nih.gov/25199044/

59. Taha NA, Abdelkhader SZ. Outcome of full pulpotomy using Biodentine in adult patients with symptoms indicative of irreversible pulpitis. Int Endod J. agosto de 2018;51(8):819-28. Doi: 10.1111/iej.12903. https://pubmed.ncbi.nlm.nih.gov/29397003/

60. Taha NA, Khazali MA. Partial Pulpotomy in Mature Permanent Teeth with Clinical Signs Indicative of Irreversible Pulpitis: A Randomized Clinical Trial. J Endod. 1 de septiembre de 2017;43(9):1417-21. Doi: 10.1016/j.joen.2017.03.033. https://pubmed.ncbi.nlm.nih.gov/28673494/

61. Asgary S, Eghbal MJ. Treatment outcomes of pulpotomy in permanent molars with irreversible pulpitis using biomaterials: A multi-center randomized controlled trial. Acta Odontol Scand. 1 de enero de 2013;71(1):130-6. DOi: 10.3109/00016357.2011.654251. https://pubmed.ncbi.nlm.nih.gov/22339289/

62. Chrepa V, Henry MA, Daniel BJ, Diogenes A. Delivery of Apical Mesenchymal Stem Cells into Root Canals of Mature Teeth. J Dent Res. 20 de julio de 2015;94(12):1653. Doi: 10.1177/0022034515596527. https://pubmed.ncbi.nlm.nih.gov/26195498/

63. Lin J, Zeng Q, Wei X, Zhao W, Cui M, Gu J, et al. Regenerative Endodontics Versus Apexification in Immature Permanent Teeth with Apical Periodontitis: A Prospective Randomized Controlled Study. J Endod. 1 de noviembre de 2017;43(11):1821-7. Doi: 10.1016/j.joen.2017.06.023. https://pubmed.ncbi.nlm.nih.gov/28864219/

64. Ng YL, Mann V, Gulabivala K. A prospective study of the factors affecting outcomes of non-surgical root canal treatment: part 2: tooth survival. Int Endod J. 2011;44(7):610-25. Doi: 10.1111/j.1365-2591.2011.01873.x. https://pubmed.ncbi.nlm.nih.gov/21366627/

65. Friedman S, Abitbol S, Lawrence HP. Treatment Outcome in Endodontics: The Toronto Study. Phase 1: Initial Treatment. J Endod. 1 de diciembre de 2003;29(12):787-93. DOi: 10.1097/00004770-200312000-00001. https://pubmed.ncbi.nlm.nih.gov/14686806/

66. Rutherford RB, Gu K. Treatment of inflamed ferret dental pulps with recombinant bone morphogenetic protein-7. Eur J Oral Sci. 2000;108(3):202-6. Doi: 10.1034/j.1600-0722.2000.108003202.x. https://pubmed.ncbi.nlm.nih.gov/10872990/

67. Crop MJ, Baan CC, Korevaar SS, IJzermans JNM, Pescatori M, Stubbs AP, et al. Inflammatory conditions affect gene expression and function of human adipose tissue-derived mesenchymal stem cells. Clin Exp Immunol. diciembre de 2010;162(3):474-86. Doi: 10.1111/j.1365-2249.2010.04256.x. https://pubmed.ncbi.nlm.nih.gov/20846162/

68. Sabeti MA, Nekofar M, Motahhary P, Ghandi M, Simon JH. Healing of Apical Periodontitis After Endodontic Treatment With and Without Obturation in Dogs. J Endod. 1 de julio de 2006;32(7):628-33. Doi: 10.1016/j.joen.2005.12.014. https://pubmed.ncbi.nlm.nih.gov/20846162/

69. Galler KM, Krastl G, Simon S, Van Gorp G, Meschi N, Vahedi B, et al. European Society of Endodontology position statement: Revitalization procedures. Int Endod J. agosto de 2016;49(8):717-23. doi: 10.1111/iej.12629. https://pubmed.ncbi.nlm.nih.gov/26990236/

70. Caviedes-Bucheli J, Muñoz-Alvear HD, Lopez-Moncayo LF, Narvaez-Hidalgo A, Zambrano-Guerrero L, Gaviño-Orduña JF, et al. Use of scaffolds and regenerative materials for the treatment of immature necrotic permanent teeth with periapical lesion: Umbrella

review. Int Endod J. 2022;55(10):967-88. Doi: 10.1111/iej.13799. https://pubmed.ncbi.nlm.nih.gov/35821587/

71. Maniglia-Ferreira C, Almeida-Gomes F, Carvalho-Sousa B, Barbosa AVH, Lins CCSA, Souza FD, et al. Clinical evaluation of the use of three anesthetics in endodontics. Acta Odontol Latinoam AOL. 2009;22(1):21-6. PMID: 19601492. https://pubmed.ncbi.nlm.nih.gov/19601492/

72. Jha P, Virdi MS, Nain S. A Regenerative Approach for Root Canal Treatment of Mature Permanent Teeth: Comparative Evaluation with 18 Months Follow-up. Int J Clin Pediatr Dent. 1 de marzo de 2019;12(3):182-8. Doi: 10.5005/jp-journals-10005-1616. https://pubmed.ncbi.nlm.nih.gov/31708612/

73. Chng HS, Pitt Ford TR, McDonald F. Effects of prilocaine local anaesthetic solutions on pulpal blood flow in maxillary canines. Endod Dent Traumatol. abril de 1996;12(2):89-95. DOi: 10.1111/j.1600-9657.1996.tb00103.x. https://pubmed.ncbi.nlm.nih.gov/9028203/

74. Petrino, J et al Challenges in Regenerative Endodontics: A Case Series | Request PDF. ResearchGate [Internet]. 22 de octubre de 2024 [citado 17 de marzo de 2025]; Disponible en: https://www.researchgate.net/publication/41508162_Challenges_in_Regenerative_Endodontics_A_Case_Series. Doi: 10.1016/j.joen.2009.10.006. https://pubmed.ncbi.nlm.nih.gov/20171379/.

75. McLean C, Reader A, Beck M, Meyers WJ. An evaluation of 4% prilocaine and 3% mepivacaine compared with 2% lidocaine (1:100,000 epinephrine) for inferior alveolar nerve block. J Endod. 1 de marzo de 1993;19(3):146-50. Doi: 10.1016/s0099-2399(06)80510-8. https://pubmed.ncbi.nlm.nih.gov/8509754/

76. Gimbel M, Correa A, Lin LM. Calcium hydroxide as a temporary filling of the post space in root-filled teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1 de julio de 2002;94(1):98-102. Doi: 10.1067/moe.2002.123865. https://pubmed.ncbi.nlm.nih.gov/12193902/

77. Mahgoub N, Alqadasi B, Aldhorae K, Assiry A, Altawili ZM, Tao Hong. Comparison between iRoot BP Plus (EndoSequence Root Repair Material) and Mineral Trioxide Aggregate as Pulp-capping Agents: A Systematic Review. J Int Soc Prev Community Dent. 13 de

noviembre de 2019;9(6):542-52. Doi: 10.4103/jispcd.JISPCD_249_19. https://pubmed.ncbi.nlm.nih.gov/32039073/

78. Parirokh M, Torabinejad M, Dummer PMH. Mineral trioxide aggregate and other bioactive endodontic cements: an updated overview – part I: vital pulp therapy. Int Endod J. 2018;51(2):177-205. Doi: 10.1111/iej.12841. https://pubmed.ncbi.nlm.nih.gov/28836288/

79. Wongwatanasanti N, Jantarat J, Sritanaudomchai H, Hargreaves KM. Effect of Bioceramic Materials on Proliferation and Odontoblast Differentiation of Human Stem Cells from the Apical Papilla. J Endod. 1 de agosto de 2018;44(8):1270-5.

80. Eraković M, Duka M, Bekić M, Tomić S, Ismaili B, Vučević D, et al. Anti-inflammatory and immunomodulatory effects of Biodentine on human periapical lesion cells in culture. Int Endod J. 2020;53(10):1398-412. Doi: 10.1016/j.joen.2018.03.014 . https://pubmed.ncbi.nlm.nih.gov/29935871/

81. Surya Raghavendra S, Jadhav GR, Gathani KM, Kotadia P. BIOCERAMICS IN ENDODONTICS – A REVIEW. J Istanb Univ Fac Dent [Internet]. 17 de noviembre de 2017 [citado 5 de marzo de 2025];51(0). Disponible en: http://iupress.istanbul.edu.tr/journal/eor/article/endodontide-biyoseramikler-derleme. Doi 10.17096/jiufd.63659. https://pubmed.ncbi.nlm.nih.gov/29354316/

82. Ríos-Osorio N, Caviedes-Bucheli J, Jimenez-Peña O, Orozco-Agudelo M, Mosquera-Guevara L, Jiménez-Castellanos FA, et al. Comparative outcomes of platelet concentrates and blood clot scaffolds for regenerative endodontic procedures: A systematic review of randomized controlled clinical trials. J Clin Exp Dent. 1 de marzo de 2023;15(3):e239-49. Doi: 10.4317/jced.60150.

83. Martin N, Mulligan S. Environmental Sustainability Through Good-Quality Oral Healthcare. Int Dent J. febrero de 2022;72(1):26-30. Doi: 10.1016/j.identj.2021.06.005. https://pubmed.ncbi.nlm.nih.gov/34412896/

84. Martin N, Mulligan S. Environmental Sustainability Through Good-Quality Oral Healthcare. Int Dent J. 16 de agosto de 2021;72(1):26-30. Doi: 10.1016/j.identj.2021.06.005. Doi: 10.1016/j.identj.2021.06.005. https://pubmed.ncbi.nlm.nih.gov/34412896/

.

85. Martin N, Sheppard M, Gorasia G, Arora P, Cooper M, Mulligan S. Drivers, opportunities and best practice for sustainability in dentistry: A scoping review. J Dent. 1 de septiembre de 2021;112:103737. Doi: 10.1016/j.jdent.2021.103737. https://pubmed.ncbi.nlm.nih.gov/34182061/

86. Duane B, Borglin L, Pekarski S, Saget S, Duncan HF. Environmental sustainability in endodontics. A life cycle assessment (LCA) of a root canal treatment procedure. BMC Oral Health. 1 de diciembre de 2020;20(1):348. Doi: 10.1186/s12903-020-01337-7 https://pubmed.ncbi.nlm.nih.gov/33261595/

ANNEXES