applied sciences

MDPI

Review

Different Approaches to the Regeneration of Dental Tissues in Regenerative Endodontics

Anna M. Krupińska [1], Katarzyna Skośkiewicz-Malinowska [2] and Tomasz Staniowski [2,*]

[1] Department of Prosthetic Dentistry, Wroclaw Medical University, 50-367 Wrocław, Poland; anna.krupinska@umed.wroc.pl
[2] Department of Conservative Dentistry and Pedodontics, Wroclaw Medical University, 50-367 Wrocław, Poland; katarzyna.skoskiewicz-malinowska@umed.wroc.pl
* Correspondence: tomasz.staniowski@umed.wroc.pl

Abstract: (1) Background: The regenerative procedure has established a new approach to root canal therapy, to preserve the vital pulp of the tooth. This present review aimed to describe and sum up the different approaches to regenerative endodontic treatment conducted in the last 10 years; (2) Methods: A literature search was performed in the PubMed and Cochrane Library electronic databases, supplemented by a manual search. The search strategy included the following terms: "regenerative endodontic protocol", "regenerative endodontic treatment", and "regenerative endodontics" combined with "pulp revascularization". Only studies on humans, published in the last 10 years and written in English were included; (3) Results: Three hundred and eighty-six potentially significant articles were identified. After exclusion of duplicates, and meticulous analysis, 36 case reports were selected; (4) Conclusions: The pulp revascularization procedure may bring a favorable outcome, however, the prognosis of regenerative endodontics (RET) is unpredictable. Permanent immature teeth showed greater potential for positive outcomes after the regenerative procedure. Further controlled clinical studies are required to fully understand the process of the dentin–pulp complex regeneration, and the predictability of the procedure.

Keywords: endodontic materials; dental tissues regeneration; dental bioengineering; pulp revascularization; pulp regeneration; regenerative endodontics; apical periodontitis treatment

Citation: Krupińska, A.M.; Skośkiewicz-Malinowska, K.; Staniowski, T. Different Approaches to the Regeneration of Dental Tissues in Regenerative Endodontics. *Appl. Sci.* **2021**, *11*, 1699. https://doi.org/10.3390/app11041699

Academic Editor: Gabi Chaushu

Received: 8 January 2021
Accepted: 11 February 2021
Published: 14 February 2021

1. Introduction

Tissue engineering is a fast-growing scientific field connecting the principles of medicine, engineering, and biology to replace, restore, or regenerate tissues damaged or lost due to disease and/or trauma [1,2]. The result of this approach relies on the essential interplay between stem cells, signaling molecules, and scaffolds; known as the classic tissue engineering triad [1]. Stem cells are defined as highly proliferative, unspecialized cells, which have the ability to differentiation into various other types of cells [3,4]. Postnatal stem cells have been identified in different body tissues, such as bone marrow, peripheral blood, hair follicles, skin, intestine, adipose tissue, pancreas, and dental tissues [5,6]. Studies indicate that dental pulp contains five types of mesenchymal stem cells (MSCs) [7], which are noteworthy because of their pluripotent properties and easy method of isolation from exfoliated deciduous teeth [8]. It has been suggested, that dental pulp stem cells have the ability to differ not only into teeth tissues, but that they also have a neuronal and muscular differentiation capacity, and thus may play a key role in the future medical treatment of various diseases [9]. The following sources of stem cells in human dental pulp have been characterized [3,10,11]:

- Dental pulp stem cells (DPSCs): Clonogenic cells with high proliferation potential and long-term self-renewal [11], isolated from permanent third molars in 2000 by Gronthos et al. They reside within niches in pulp chambers [8] in a stable microenvironment,

which depends on the interplay between growth factors, extracellular matrix proteins, receptor molecules, and stem cells [5]. Research has indicated that dental pulp stem cells have the ability to become odontoblast-like cells and generate ectopic dentin in the subcutaneous tissues of immunocompromised mice [12,13]. Furthermore, it was shown that DPSCs can differentiate into other non-dental cells, such as osteoblasts, odontoblast, chondrocytes (thus, they can produce bone and cartilage tissues), neuron cells, adipocyte, cardiomyocytes, and insulin-secreting Beta cells [5,14].

- Stem cells from exfoliated deciduous teeth (SHED): Isolated by Miura et al., exhibiting multipotential differentiation properties and increased cell-population doublings in comparison to DPSCs [15]. It is hypothesized that SHED cells have an extensive proliferation ability higher than DPSCs and MSCs derived from bone marrow, due to being a more immature population [16].
- Stem cells from apical papillae (SCAP): MSC-like cells located in the tooth root apex, discovered for the first time by Sonoyama et al. in the apical papilla of human immature permanent teeth [12]. Studies performed in immunocompromised rodents showed the odontogenic potential of SCAP cells when multipotent stem cells were transplanted with hydroxyapatite/tricalcium phosphate particles. The regeneration of pulp-like tissue and dentin structure were observed [17]. According to the conducted scientific studies, it is believed that SCAP cells are involved in the formation of root dentin, as a source of primary odontoblast [18], opposed to DPSCs, which take part in reparative dentin formation, providing replacement odontoblast [19]. It is also hypothesized that a positive result of endodontic treatment of infected immature permanent tooth may be achieved due to the reservoir of SCAP in the apical papilla, and their ability to produce primary odontoblasts involved in apexogenesis [12,20,21].
- Periodontal ligament stem cells (PDLSCs): These multipotent cells have the potential to develop into cementoblast-like cells, adipocytes, and chondrogenic cells. In vivo experiments have exhibited PDLSC's capacity to form cementum/PDL-like structures [22,23]. Therefore, using these cells in periodontal regeneration protocols is being considered [24].
- 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. The latter are usually extracted and disposed of, therefore there are no controversial ethical issues linked to the sourcing of DFPCs [25]. Some studies have shown that DFPCs can transform into fibroblasts, osteoblasts, periodontal ligament, and cementoblasts [26], thus these cells may be useful in regeneration therapies of periodontal tissues [5].

Tissue regeneration requires the appropriate signals (growth and differentiating factors) that activate these cells [27]. Growth factors are extracellular proteins or polypeptides, which interact with specific-cell receptors to activate intracellular signaling cascades, eventuating in cell proliferation, differentiation, migration, and the apoptosis of numerous different cell types, including dental pulp cells and stem cells [28]. Growth factors differ in their functions, thus they may be used in many biomedical applications. Stimulation of cellular division and differentiation are coordinated by several growth factors, such as fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like factor (IGF) [28]. Others are known as wound-healing promoting factors, as in the case of TGF-β superfamily-types 1, 2, and 3 [29]. Most of these bioactive molecules are also released by odontoblast cells and fixed in the dentin matrix during tooth morphogenesis [30]. Scientific research has revealed that growth factors like PDGF, TGF, IGF-1, EGF, and FGF may participate in dentin regeneration processes when damage occurs [31], furthermore, the important role of these signaling molecules in stem cell maintenance and their contribution to dental tissues regeneration was considered. Moreover, two distinct families of growth factors, crucial for tooth formation and regeneration, are vascular endothelial growth factor (VEGF) and bone morphogenetic protein (BMP) [32,33]. VEGF, also known as vascular permeability factor (VPF), is a major

angiogenic factor, with a specific affinity to endothelial cells (ECs). The function of VEGF activates blood vessel formation and homeostasis by stimulating migration, proliferation, and increased survival of endothelial cells in the hypoxic environment [7,34]. It is well accepted that the vascular network, in providing oxygen and nutrients, is essential for tissue development and repair, and thus VEGF may be a beneficial element for pulp regeneration [35]. BMPs belong to the transforming growth factor-β (TGF-β) superfamily of proteins, and are responsible for diverse biological functions. They act as potent regulators of proliferation, migration, and differentiation of MSCs into osteoblasts and chondroblasts, and thus they play a pivotal role in skeletal development [18,36]. In addition, in vivo and in vitro studies have shown the requirement of BMP activity in the early stages of odontogenesis [37], due to its ability to induce the transformation of pulp stem cells into odontoblasts [28]. Based on past findings, it has been suggested that BMPs may be a key element for dental tissue regeneration, especially recombinant human BMP-2, by virtue of its capability to convert adult pulp progenitor cells into odontoblast-like cells [38]. Studies conducted in animal models, including dogs, macaques, rats, and ferrets, revealed positive results for dentin formation when BMP-7 was placed in capping material over amputated dental pulp [28]. Interestingly, there are various recognized localizations of the reservoir of growth factors for endodontic therapies: the dentin matrix, platelet-rich fibrin, platelet-rich plasma, and blood clots [31,39,40].

As a third component in the tissue engineering triad, the scaffold is described as a three-dimensional (3D) biocompatible material that provides mechanical support for bioactive molecules or cells, and acts as an extracellular matrix template, predisposing the adhesion and proliferation of a specific cell type [41], such as pulpal cells. Ideally, the scaffold should have high porosity to facilitate cells deposition, and to permit effective nutrient and gas exchange. Moreover, it should have the proper physical and mechanical properties, and also be entirely biodegradable. However, the scaffold degradation must be equal to a formation rate of new tissue [42,43]. There are various types of scaffolds known, based on their origin; natural scaffolds (e.g., collagen, hyaluronic acid, PRF, PRP, blood clot, chitosan) and artificial scaffolds (e.g., polymers of polyglycolic acid, polylactic acid, polyepsiloncaprolactone, glass–ceramic, and bioactive glasses) [18,42,44] differ in attributes and properties. Scaffold technology has shown promising advancements in regenerative dentistry, scientifically demonstrated in immunodeficient mice. The researchers obtained a regeneration of dentin-like tissue in disinfected and emptied root canal using a porous polymer scaffold seeded with stem cells, after transplantation into an animal model [45,46].

The development and achievements of tissue engineering have provided novel perspectives and treatment options in endodontics for the repair of the pulp–dentin complex, cementum, and periodontal tissues [47]. According to The American Association of Endodontists (AAE), regenerative endodontics is defined as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp dentin complex" [35]. It is accepted that nonsurgical root canal therapy treatment and regenerative endodontic procedures (REP) have the same essential aim. Nevertheless, in traditional root canal treatment, the canal space is filled with foreign material, and in regenerative procedures, vital host tissue in the tooth canal is created [48], which has the ability to coordinate local immune system functions and fight bacterial infections. Regenerative endodontics brings a new perspective to treating teeth with necrotic pulp; and, furthermore, uncomplicated and inexpensive procedures can be conducted with currently used instruments and materials [49,50]. Even though, the pioneering experiments in regenerative endodontics (RET) were carried out in the 1960s by Nygaard-Ostby, and despite there still being clear interest and progress in this dentistry field, there is no established standardized clinical protocol for RET [51]. In 2016, the European Society of Endodontology (ESE) [52] and the American Association of Endodontists (AAE) [53] released a clinical consideration of the regenerative procedure, however, the AAE pointed out that there are many possibilities for treatment, and that further research and reviews are needed. Thus, this review aimed to analyze selected case reports and case series conducted

in the last 10 years, to provide a summary of the different approaches to regenerative endodontics. The regenerative procedure has established a new approach to root canal therapy, to preserve the vital pulp of the tooth. The presentation of numerous clinical cases allows the reader to compare the applied treatment protocols from the perspective of his own patients, and to modify his treatment methods in comparison with other dentists. The findings of this review emphasize the increasing popularity of regenerative endodontics, with the simultaneous indication of its limitations.

2. Materials and Methods

What are the differences in regenerative endodontic treatment methods, based on selected clinical cases and the available literature?

In accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [54], an ample search was conducted through electronic databases of scientific and medical literature including "PubMed" and the "Cochrane Library". The search strategy included the following keywords: "regenerative endodontic protocol", "regenerative endodontic treatment", and "regenerative endodontics" combined with "pulp revascularization". Furthermore, a manual method was carried out for possible additional studies. The inclusion criteria were in vivo studies in which regenerative procedures were performed in immature and mature permanent teeth, with or without apical periodontitis. The exclusion criteria were: reviews and studies not in the English language, studies in animals, and studies published before 2009. Obtained studies were analyzed, and articles not meeting the applied criteria were excluded. The initial identification included the titles and abstracts of articles on regenerative endodontics: studies identified by searching databases (n = 346); PubMed (n = 250), Cochrane Library (n = 96), and studies identified through manual searching (n = 40). The reduction was made by excluding nonrelevant titles from the literature review and papers published before 2009. Subsequently, the number of articles was reduced by rejecting nonrelevant abstracts, duplicates, review articles, research on animals, and papers not in English. That resulted in 58 full-text articles being assessed for eligibility. Further selection required meticulous reading of full-text publications and excluding papers with observations shorter than 5 months, and with incomplete information about irrigants, root canal fillings, and scaffolds. Full-text publications were read in order to extract the following data: patient age, kind of tooth, root canal disinfection protocol and size of apical foramen, inter-visit medicaments, scaffold and capping material, recall time, and procedure outcome (Figure 1).

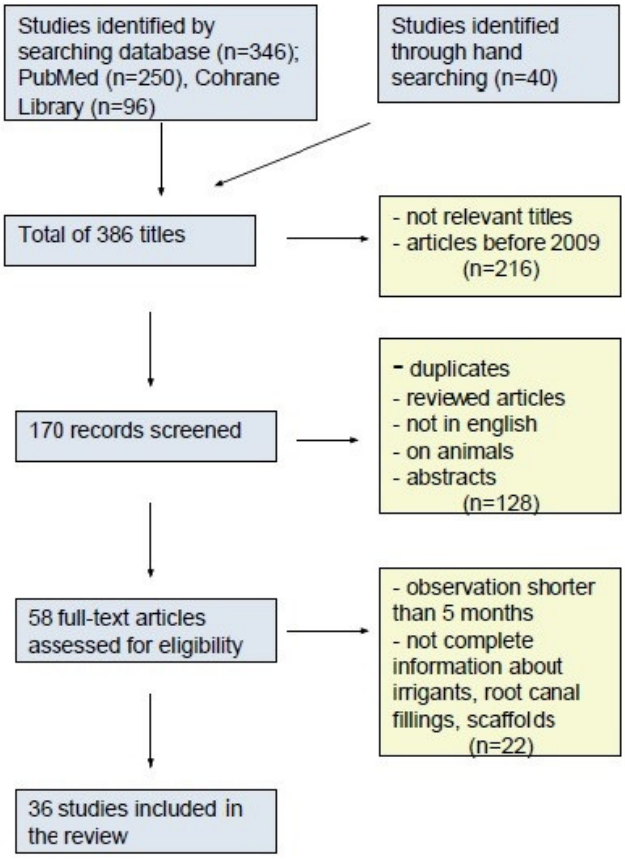

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow diagram of the article selection [54].

3. Results

The search of the mentioned two databases and manual searching retrieved 386 studies. After the removal of duplicate articles and screening by title and abstract, 36 case reports were selected. Retrieved data from the analyzed studies are described in Table 1.

In the articles collected, patients' age ranged from 6 to 25 years old. Most of the reports presented patients under 15 years old, and only seven studies described patients above 20 years old. The total number of evaluated teeth was 84. Most cases described immature teeth (n = 71). Anterior teeth were mainly examined (n = 58), followed by premolars (n = 17) and molars (n = 9). Root canal disinfection was commonly performed with sodium hypochlorite (NaOCl) in a concentration ranging from 1–5.25%, with minimal or no mechanical instrumentation. In 72.6% of the teeth (n = 61) triple antibiotic paste (TAP) was used as an intracanal medication, and alternatively to TAP, double antibiotics paste (DAP) was used in 2.4% of teeth (n = 2) to prevent crown tooth discoloration. Calcium hydroxide ($Ca(OH)_2$) paste was used in 13.1% of teeth (n = 11), and methapaste in 8.3% of teeth (n = 7). While, 3.6% of teeth (n = 3) were treated with a one-visit protocol, without intracanal medicament.

Table 1. Retrieved data from the studies that met the inclusion criteria.

Case No.	Patient Age	Tooth/Tooth Number	Root Canal Irrigants	Inter-visit Root Canal Filling	Scaffold; Capping Material	Recall	Results	References
1	7	Permanent immature with apical periodontitis/#36	2.5% NaOCl, 20% EDTA activated with EndoActivator in the coronal third	Calcium hydroxide	Blood clot; MM-MTA (Micro-Mega, Besançon CEDEX, France)	2 y	The patient was reviewed after 3, 9, 12 and 24 months: -asymptomatic -physiological mobility -normal reaction to percussion and palpation -9 m: complete periapical healing, apical closure -1 y: increase in root length, dentin thickness -2 y: CBCT(cone-beam computed tomography): complete periapical healing, apical foramen closure of the both mesial canals and distolingual canal, resolution of the periapical lesion of the distobuccal canal, not completed apical closure	Ajram J et al. [55]
2	15	Permanent mature/#13	5.25% NaOCl, 17% EDTA	Double Antibiotics Paste (DAP)	Blood clot; Mineral trioxide aggregate (MTA)	30 m	-3 m: asymptomatic, no response to vitality testing -6 m: nearly normal reaction to the electric pulp tester -12 m: positive response to pulp vitality testing, root wall thickening -30 m: normal reaction of pulp vitality	Qingan Xu et al. [56]
3	21	Permanent mature with apical periodontitis / #21, #22	5.25% NaOCl, saline, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; ProRoot MTA (Dentsply Tulsa Dental, Tulsa, OK, USA)	5 y	-1 m: asymptomatic, decreased apical radiolucency, negative response to the cold test and the electric pulp test -5 y: asymptomatic, complete resolution of the apical lesion	Nagas E et al. [57]
4	7	Permanent immature with apical periodontitis—retreatment of failed revitalization / #11	5% NaOCl ultrasonically activated for 5 min, saline, 17% EDTA	Calcium hydroxide	Blood clot; White MTA (ProRoot MTA; Dentsply Tulsa Dental, Johanson City, TN)	15 m	The recall visits were performed after 3, 5, 9, 12, and 15 months. -asymptomatic -negative response to cold or heat vitality tests -normal reaction to percussion and palpation tests -decrease in periapical lesion and root development -new mineralized tissue in contact with MTA	Žižka R et al. [58]
5	18	Permanent immature with apical periodontitis / #11	1% NaOCl, 17% EDTA	Calcium hydroxide (Prime Dental products, Mumbai, India)	Human Amniotic Membrane (ACTREC, Tata memorial hospital tissue bank, Mumbai, India); Biodentine (Septodont, France)	3 y	The patient was reviewed after 15 days, 3 months, 19 months, and 36 months. -asymptomatic -pulp responded to vitality tests -healing of apical lesion and thickening of dentinal walls	Suresh N et al. [59]
6-I	24	Permanent mature with apical periodontitis/#21	1.5% NaOCl, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; MTA (MTA Angelus)	9 m	-a decrease in size of radiolucency -asymptomatic -no sensitivity to percussion and palpation -sinus tract healed -normal probing depths -physiological mobility -negative response to pulp tests	Rasha A. Abou Samra et al. [60]
6-II	25	Permanent mature with apical periodontitis / #11	1.5% NaOCl, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; MTA (MTA Angelus)	9 m	The patient was recalled at 3, 6 and 9 months after treatment. -asymptomatic -negative reaction to pulp vitality tests -healing of apical lesion -normal reaction to percussion	Rasha A. Abou Samra et al. [60]

Table 1. *Cont.*

Case No.	Patient Age	Tooth/Tooth Number	Root Canal Irrigants	Inter-visit Root Canal Filling	Scaffold; Capping Material	Recall	Results	References
6-III	20	Permanent mature with apical periodontitis / #31	1.5% NaOCl, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; MTA (MTA Angelus)	9 m	The follow-up visits were performed at 3, 6 and 9 months after treatment. -reduction of apical radiolucency size -no reaction to pulp vitality tests -normal probing depths	Rasha A. Abou Samra et al. [60]
7	10	Permanent immature with apical periodontitis / #11	1.5% NaOCl, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; Mineral trioxide aggregate (MTA; Dentsply Tulsa Dental, Tulsa, USA)	5 m	-2 m: resolution of the apical lesion, apex closure, increased width of root walls, positive response to pulp vitality testing. -5 m: apex closure, positive response for vitality testing	Moodley, Desi Patel et al. [61]
8	23	Permanent immature with apical periodontitis / #45	2.5% NaOCl, 17% EDTA, sterile saline	Triple Antibiotics Paste (TAP)	Blood clot and PRF(platelet rich fibrin); MTA(ProRoot MTA, Dentsply)	1 y	-8 m: asymptomatic, healing of periapical radiolucency -12 m: apical radiolucency not completely eradicated	Gürhan C et al. [62]
9	8	Permanent immature with apical periodontitis / #46	5% NaOCl	Triple Antibiotics Paste (TAP)	Blood clot; Mineral trioxide aggregate (MTA)	1 y	-complete healing apical lesion -root canal walls thickening and -foramen apex progressed in closing	López Carmen et al. [63]
10	8–11	Permanent immature teeth with apical periodontitis / 24 incisors, 6 premolars	2.5% NaOCl, sterile saline, 0.12% CHX, 17% EDTA	Triple Antibiotics Paste (TAP)	PRF; White MTA Dentsply Tulsa Dental, Tulsa, OK)	1 y	-1 m: asymptomatic -12 m: resolution or decreasing in the apical lesion, negative response to percussion and palpation tests	Alagl A et al. [64]
11	8	Permanent immature with apical periodontitis / #21	5.25% NaOCl, sterile saline, 17% EDTA	Calcium hydroxide	Blood clot; Biodentine	2 y	Time points for recall were at 1, 3, 6 and 12 months. -apical closure -no response to cold or electric test	Marc Llaquet et al. [65]
12	16	Permanent immature with apical periodontitis / #21	5.25% NaOCl, 0.2% CHX	Triple Antibiotics Paste (TAP)	Blood clot; MTA(ProRoot MTA, Dentsply)	6 m	-3 m: asymptomatic -6 m: root maturation, healing of the radiolucent lesion	Rasika Kashikar et al. [66]
13	13	Permanent immature with apical periodontitis / #35	5.25% NaOCl	Triple Antibiotics Paste (TAP)	Blood clot; MTA(ProRoot MTA, Dentsply)	1 y	-asymptomatic -positive response to electrical test -apical radiolucency resolved completely -no increase in root length and root wall thickness	Merve Erkmen Almaz et al. [67]
14	8	Permanent immature with apical periodontitis / #11	1.5% NaOCl, normal saline	Triple Antibiotics Paste (TAP)	Blood clot; White MTA (Proroot MTA, Densply)	1 y	Recall visits were after 1, 3, 6, 9, and 12 months. -negative response to percussion and palpation tests -negative response to heat or an electric pulp tester (EPT) -root lengthening -thickening of the dentinal walls - apical closure -healing of the periapical lesion	Amitava Bora et al. [68]
15	8–21	Permanent mature with apical periodontitis / 4 anterior and 3 molar teeth	2.5% NaOCl, 17% EDTA	Metapaste (Meta Biomed Co, Ltd., Chungbuk, Korea)	Blood clot; MTA (ProRoot MTA, Dentsply)	8–26 m	-apical lesion healed in two teeth and healing in 5 teeth -no response to cold or electric pulp tester tests -asymptomatic	Tarek Mohamed Saoud et al. [69]
16	12	Permanent immature with apical periodontitis / #15	3% NaOCl, sterile saline	Calcium hydroxide (Calasept, Nordiska Dental, Ängelholm, Sweden)	Blood clot; Grey MTA (ProRoot, Dentsply Tulsa Dental, Johnson City, TN, USA)	5.5 y	The patient was recalled after 4, 7, 18, 36, and 66 months -asymptomatic -4 m: decreasing of the periapical lesion -7 m: positive response to cold and electric pulp tests, root growth - 18 m: apical closure -3 y and 5.5 y: severe calcification of the canal, greyish discoloration of the cervical region of the crown	She CM et al. [70]

Table 1. *Cont.*

Case No.	Patient Age	Tooth/Tooth Number	Root Canal Irrigants	Inter-visit Root Canal Filling	Scaffold; Capping Material	Recall	Results	References
17	12	Permanent immature with apical periodontitis, endodontically treated / #11	5.25% NaOCl, sterile saline, 0.12% CHX	Double Antibiotics Paste (DAP)	Blood clot; CollaPlug (Zimmer Dental, Carlsbad, CA, USA), MTA (MTA-Angelus, Angelus, Londrina, PR, Brazil)	3 y	-3 m and 6 m: asymptomatic -1 y: radiolucency healing -3 y: asymptomatic, root apex closed	Al-Tammami MF et al. [71]
18	13	Permanent immature with apical periodontitis / #37	5.25% NaOCl, saline	Triple Antibiotics Paste (TAP)	PRF; Biodentine (Septodont, France)	1 y	Follow-up visits conducted after 3, 6, 9, and 12 months. -asymptomatic -9 m: positive response to sensibility tests -root lengthening and canal walls thickening - apical closure	Subash D et al. [72]
19	11	Permanent immature / #45	5.25% NaOCl, 17% EDTA, saline, 2% CHX	(one visit)	Blood clot; Biodentine (BD, Septodont, Saint Maur des Fosses, France)	2 y	-decreasing of periapical lesion -complete root maturation -no pain -healed sinus tract	Aldakak MM et al. [73]
20	6	Permanent immature with apical periodontitis / #21	3% NaOCl	Calcium hydroxide (Fórmula & Ação, São Paulo, Brazil)	Blood clot; Collagen matrix (Hemospon; Technew Ind. & Comercio, Rio de Janeiro, Brazil), MTA (Angelus; Londrina, Paraná, Brazil)	3 y	-6 m: root canal lengthening, absence of radiolucency -3 y: asymptomatic, crown discoloration, closed root apex	Silva MH et al. [74]
21	14	Permanent immature with apical periodontitis / #11	5.25% NaOCl, saline, 0.2% CHX	Triple Antibiotics Paste (TAP)	PRF; Gray MTA (ProRoot MTA, Dentsply)	14 m	The patient was recalled after 3, 6, 9, 12, and 14 months. -asymptomatic -negative reaction to palpation and percussion tests -regression of periapical lesion -root apex closure	Faizuddin U et al. [75]
22	8	Permanent immature / #14	5.25% NaOCl	Calcium hydroxide (Vitapex; Neo Dental Chemical Products, Tokyo, Japan)	Blood clot; ProRoot MTA (Dentsply Maillefer, Ballaigues, Switzerland)	3 y	-3 m: asymptomatic -6 m: root length increasing -12 m: asymptomatic, complete root development -36 m: apical closure	Al-Ghamdi NS et al. [76]
23	14	Permanent immature with apical periodontitis, endodontically treated / #11	2.5% NaOCl ultrasonically activated for 60 s, 17% EDTA	Triple Antibiotics Paste (TAP)	Blood clot; a sterile collagen membrane barrier (Collacote, Zimmer Dental, Carlsbad, CA, USA), MTA Dentsply Tulsa Dental, Tulsa, OK)	3 y	-2 y: radiolucent lesion healed -3 y: asymptomatic, apical closure -no signs of thickening of canal walls and root lengthening -negative response to the cold test	Maria-Elpida A. Miltiadous et al. [77]
24	10	Permanent immature / # 11	5.25% NaOCl	Triple Antibiotics Paste (TAP)	Blood clot; White MTA (Angelus)	1 y	-asymptomatic-normal response to percussion -normal probing depths -normal tooth mobility -negative response to cold test or EPT -increased root length -root wall thickening	Chandran V et al. [78]
25	11	Permanent immature with apical periodontitis / #11, #21	3% NaOCl, saline	Triple Antibiotics Paste (TAP)	Blood clot; MTA	6 m	-no swelling, no pain -reduced tooth mobility -negative response to electrical or thermal tests -decrease of radiolucency -progressive root maturation	Aggarwal, Gaurav et al. [79]

Table 1. *Cont.*

Case No.	Patient Age	Tooth/Tooth Number	Root Canal Irrigants	Inter-visit Root Canal Filling	Scaffold; Capping Material	Recall	Results	References
26	9	Permanent immature dens invaginatus with apical periodontitis / #12	2.5% NaOCl, saline	Calcium hydroxide (Sultan Chemists Inc., Englewood, NJ, USA), after 3 weeks—Triple Antibiotics Paste (TAP)	Blood clot; MTA (MTA-A; Angelus, Londrina, Brazil)	20 m	-12 m: complete healing of the periapical lesion, the apical foramen remain open, negative response to vitality testing -20 m: apical closure.	Kaya-Büyükbayram I et al. [80]
27	9	Permanent immature with apical periodontitis / #11 #21	5.25% NaOCl, saline	(one visit)	PRF; MTA(ProRoot MTA, Dentsply)	10 m	-6 m: negative response to percussion and palpation tests, asymptomatic, root lengthening, thickening of the dentinal walls, decreasing of the apical lesion. -10 m: complete apical closure, negative response to electric pulp test	Johns DA et al. [81]
28	10	Permanent immature with apical periodontitis / #35	2.5% NaOCl	Triple Antibiotics Paste (TAP)	PRP (platelet rich plasma); MTA(ProRoot MTA, Dentsply)	2 y	-6 m: asymptomatic, root development, healed apical radiolucency -2 y: root fully developed	Güven Polat G et al. [82]
29	12	Permanent immature with apical periodontitis / # 35	2.5% NaOCl, sterile saline, 2% CHX	Triple Antibiotics Paste (TAP)	Blood clot; MTA	1 y	-3 m: asymptomatic, no sinus tract, healing of the radiolucency -6 m: continuation of apex development -1 y: closure of the apex, and dentinal walls thickening, below the MTA a mineralized bridge developed	Raju SM et al. [83]
30	9	Permanent immature with apical periodontitis / #11, #21	5.25% NaOCl, saline	Triple Antibiotics Paste (TAP)	Blood clot; White MTA	18 m	The patient was follow-up after 6, 12, and 18. -asymptomatic -apical closure -increased root length -complete healing of periapical lesion	Forghani M et al. [84]
31	11	Permanent immature with apical periodontitis / #21	2.5% NaOCl	Triple Antibiotics Paste (TAP)	PRF; MTA	1 y	The tooth was reviewed after 6 and 12 months. -asymptomatic -negative response to palpation and percussion tests -positive reaction to cold and electric sensitivity tests -root development -apical closure -resolution of apical lesion	Mishra N et al. [85]
32	12	Permanent immature with apical periodontitis / #35	3% NaOCl, sterile saline	Triple Antibiotics Paste (TAP)	Blood clot; MTA (Dentsply Tulsa Dental, Johnson City, TN, USA)	2 y	-6 w: reduced the periapical lesion -2 y: complete root apex closure, increase in root wall thickness and in root length	Kim DS et al. [86]
33	24	Permanent immature with apical periodontitis / #21	5.25% NaOCl, distilled water, with 2% CHX	Triple Antibiotics Paste (TAP)	Blood clot; White MTA (ProRoot, Dentsply/Tulsa Dental, Tulsa, OK, USA)	2 y	-dentinal walls thickening-root end closure and root elongation -apical lesion healed	Aggarwal V et al. [87]
34	8–11	Permanent immature with apical periodontitis / #26, #46, #47	2.5% NaOCl, sterile saline	$Ca(OH)_2$ powder (Merck, Darmstadt, Germany)	Blood clot; MTA (Dentsply Tulsa Dental, Tulsa, OK)	10 m	-thickening of root canal walls -continued apical development -asymptomatic -periapical lesion healing	Cehreli ZC et al. [88]
35	12	Permanent immature with apical periodontitis / #35	1% NaOCl	Triple Antibiotics Paste (TAP)	Blood clot; ProRoot white MTA (Dentsply Tulsa Dental, TN, USA)	18 m	-asymptomatic -positive response to electric pulp vitality testing -normal reaction to percussion and palpation -root maturation -healing of the apical lesion	Thomson A et al. [89]

Table 1. *Cont.*

Case No.	Patient Age	Tooth/Tooth Number	Root Canal Irrigants	Inter-visit Root Canal Filling	Scaffold; Capping Material	Recall	Results	References
36-I	13	Permanent immature with apical periodontitis / #11, #21	5.25% NaOCl, saline, 0,12% CHX	Triple Antibiotics Paste (TAP)	Blood clot; White MTA (Dentsply Tulsa Dental, Tulsa, OK)	1 y	-asymptomatic -normal reaction to percussion and palpation -probing depths in normal limits -healing of the radiolucent lesions -#21: increased thickness of the apical area -#11: lack of increase in the thickness of the root walls or in the length of the root; no response to vitality testing	Petrino J et al. [90]
36-II	11	Permanent immature with apical periodontitis / #45, #35	5.25% NaOCl, saline, 0,12% CHX	Triple Antibiotics Paste (TAP)	Blood clot; CollaPlug (Zimmer Dental, Carlsbad, CA, USA), MTA (Dentsply Tulsa Dental, Tulsa, OK)	1 y	-asymptomatic -normal reaction to percussion or palpation -periapical lesions decreasing -root walls thickening -root length increasing -positive reaction to vitality testing	Petrino J et al. [90]
36-III	6	Permanent immature with apical periodontitis / #11, #21	5.25% NaOCl, saline, 0.12% CHX	Triple Antibiotics Paste (TAP)	Blood clot; CollaPlug (Zimmer Dental, Carlsbad, CA, USA), MTA (Dentsply Tulsa Dental, Tulsa, OK)	6 m	-asymptomatic -no reaction to palpation and percussion -healing of apical lesion -root walls thickening -increase in root length -negative response to vitality testing	Petrino J et al. [90]

After periapical tissue laceration, the created blood clot was utilized as a scaffold in 54.8% of treated teeth (n = 46), and blood clot supplementation with platelet rich fibrin (PRF) was only described in one case. In five studies platelet rich fibrin (PRF) was applied as a scaffold in 35 teeth. Additionally, one study reported the use of platelet rich plasma (PRP), and another one described using human amniotic membrane as a scaffold. The most used scaffold capping material was mineral trioxide aggregate (MTA), reported in 95.2% of teeth (n = 80). From these, in seven teeth MTA was preceded by a collagen membrane, such as CollaPlug™ or Collacote™. In other studies, biodentine was used as an alternative. Follow-up periods ranged from 5 months to 66 months, and included clinical and radiographic examinations. In the reviewed articles nine immature teeth and one mature tooth showed positive teeth response to pulp vitality testing, mostly at 12-month recall; however, some studies revealed pulp vitality at 9-month, 7-month, and 2-month follow-up visits. As an outcome of regenerative endodontic treatment, almost 39% of studies reported a negative response to pulp vitality tests, and the others did not provide this information. More than 70% of the analyzed clinical cases indicated further root development after the regenerative endodontic procedure. Decrease of periapical lesions, completely healed apical periodontitis, and asymptomatic teeth were reported.

4. Discussion

The American Association of Endodontists has set three goals, whose achievement determine the degree of success of regenerative therapy. The primary goal is the elimination of periapical periodontitis and clinical symptoms. The secondary desirable goal is the thickening of root walls and/or continued root maturation. Finally, the third goal is a positive response to pulp sensibility testing [53]. There have also been requirements set that must be met by a selected case in order to start the RET procedure. The basic stipulation is a permanent tooth with necrotic pulp and immature root that does not need a post for final restoration [51]. The treated patient should be compliant and not exhibit signs of allergy to medicaments used during the procedure [49].

A complete endodontic diagnosis includes preoperative radiographic examination, thermal sensitivity pulp tests, electric pulp testing, and percussion testing [91]. Extraoral and intraoral examinations must be conducted to check for signs of lymphadenopathy or swelling. The positive result of the regenerative protocol depends on various circumstances, which are considered below. An infected immature permanent tooth with an open apex exhibits greater potential to achieve a positive result of endodontic treatment than mature teeth, due to rich vascularization, a significant supply of dental pulp stem cells (DPSC) [61], the reservoir of stem cells from apical papillae (SCAP), and their ability to produce the primary odontoblasts involved in apexogenesis [12,20,21,92]. However, one of the major problems of necrotic immature teeth is controlling the infection by obtaining a complete eradication of bacterial biofilm in the complex root canal system. In cases of atypical root canal morphology accurate treatment planning is now facilitated by the possibility of performing non-invasive three-dimensional imagining with micro-computed tomography (microCT), cone-beam computed tomography (CBCT), peripheral-quantitative computed tomography (pQCT), and spiral computed tomography [93,94]. The intracanal disinfection is considered to be an essential step of regenerative dentistry, due to the fact that infection prevents pulp tissue reparation and regeneration, and also may cause the damage of stem cells in periapical tissues [95,96]. Careful selection of irrigants seems to be significant, because of their various antimicrobial properties, different reaction with tissues, root canal lubrication, and debris removal [97,98]. The most common protocol to control infection is root irrigation with sodium hypochlorite (NaOCl) and EDTA or chlorhexidine, then canal system filling with antibacterial $Ca(OH)_2$ or triple antibiotic paste [99]. The major irrigation solution in endodontic treatment is sodium hypochlorite, with a broad antibacterial and antifungal spectrum. In vitro studies showed that NaOCl in a concentration ranging from 1% to 5.25% is effective against biofilm formed by highly resistant *Enterococcus faecalis*, however, a large amount of the solution, and irrigation time up to 5 min, are

required [49,100]. Moreover, a recent study proved that the impact of NaOCl on the mechanical properties of dentin depends on concentration and irrigation time [101]. It is also well accepted that higher concentrations of sodium hypochlorite have a toxic effect on the survival of stem cells from the apical papilla (SCAP). Therefore, current regenerative endodontics guidelines recommend using 1.5%–3% NaOCl [52,53], as this concentration of the irrigant exhibited minimal harmfulness for SCAP and odontoblasts [102]. The noxious effect of NaOCl could be reversed by the usage of 17% EDTA after NaOCl irrigation, thus it may be beneficial for tissue preservation, as well as to enhance SCAP survival [103]. In contrast to sodium hypochlorite, EDTA has the ability for smear layer removal from instrumented root canal walls. In addition, research has demonstrated that EDTA solution significantly increases the release of growth factors into root canal space, and might, therefore, play a role in the promotion of cells to recruitment and differentiation [49,104,105]. In 2016, Zeng et al. showed that irrigation of either 1.5% NaOCl + 17% EDTA, or 2.5% NaOCl + 17% EDTA significantly enhanced the release of TGFb1 in comparison with the result of irrigation only, with 17% EDTA. This resulted in the migration of dental papilla stem cells (DPSC) on the growth factors inside the root canal [31]. It is worth mentioning that a recent study on the immunohistologic analysis of failed cases indicated that intraradicular disinfection may not be efficient for preventing extraradicular biofilm formation, which may result in the persistence of apical inflammation [106].

According to a data analysis performed by Kontakiotis et al., in 68% of clinical case reports there was no mechanical instrumentation of the canal walls [107]. Some studies have suggested that complete instrumentation may be unfavorable for regenerative treatment, by removing vital tissues from the apical area of the canal and also weakening root walls [49,108]. Nevertheless, mechanical debridement seems to be required for biofilm structure removal, because its remaining causes persistent inflammation, and significantly decreases the chance of regenerative procedure success [104,109]. Zhujiang and Kim's recent case report presented a regenerative endodontic treatment for an immature necrotic #18 tooth with arrested root development. At the first appointment, the mesial canals were instrumented to the working lengths to size 45 K-file, and the distal canal to size 120 K-file. At the second appointment, each canal was formed into a 0.05 taper with K-files by step-back preparation [109]. Another study, conducted on seven permanent teeth with necrotic pulps and apical periodontitis, included mechanical instrumentation with hand K-files to #20, and following preparation with Pro-Taper Universal rotary files, also to #20 to the working length on the first visit. On the second treatment visit the canals were enlarged with rotary files to #40, #30, and #20 tip size, depending on the tooth and root location, and then the patency of the canal foramen was checked with a #15 K-file [69]. Both clinical studies achieved symptoms of remission and apical lesion healing. The apical foramen width seemed to affect the outcomes of RET in teeth with necrotic pulp, nevertheless, the minimum diameter has not been determined. It was found in an animal study that revascularization can occur with an apical foramen as small as 0.32 mm [110]. It was suggested that the large size of the apical foramen may be beneficial for cell migration from the apical area into the root canal, to create a new tissue [51]. There are different data available that show various approaches to apical foramen size preparation; e.g., Saoud and al. [111] enlarged the foramen to a #35 K-file, and Paryani and Kim [112] to a #60 K-file. Recent studies demonstrated that the most successful treatment was conducted with a foramen width of 0.5–1.0 mm [113].

To sustain disinfection and curative processes during the inter-visit period, it is necessary to fill prepared root canals with canal medications. The American Association of Endodontists proposed using in REP, either a calcium hydroxide paste or an antibiotic paste [53]. The antibiotic medicament, commonly known as a triple antibiotic paste (TAP), contains a combination of ciprofloxacin, minocycline, and metronidazole. Even though TAP exhibits a wide antibacterial spectrum [114], and numerous case reports involving antibiotic root dressing have demonstrated a positive outcome of regenerative procedures [49], TAP has some disadvantages worth consideration. Antibiotic usage is always associated

with the risk of systemic allergic reaction [51]. Tooth structure discoloration is one of the side effects caused by the minocycline included in triple antibiotic paste [115]. It could be avoided by replacing minocycline with cefaclor [116], or removed in double antibiotic paste (DAP) [117,118]. Recent research has indicated that both TAP and DAP decrease the survival of stem cells of the apical papilla (SCAP) when used in a concentration greater than 1000 mg/mL as a canal dressing [114,119]. The other recommended canal medication, calcium hydroxide, showed improvement of SCAP proliferation [103,120] and no cytotoxic properties [119]. Calcium hydroxide preserves its antimicrobial character over long periods, thus it effectively eradicates bacteria from the infected root dentine [121,122]. Andreasen et al. reported that usage of calcium hydroxide as a canal dressing for a long period of time may lead to weakening root dentine and increasing the possibility of root wall fracture [123]. Nevertheless, the latest study on root susceptibility to fracture after long-term calcium hydroxide treatment, revealed that root fracture might be more associated with root stage development than the use of the examined material [124]. It was suggested that the intracanal medicaments recommended in current standardized regenerative treatment do not achieve adequate elimination of bacteria in simulated necrotic immature root canals [125]. The next step in REP is the periapical tissues laceration with a hand file to induce bleeding into the canal space. This procedure should be carried out with local anesthesia, and without a vasoconstrictor. The flowing blood may bring mesenchymal stem cells [126], immunoglobulins, cytokines, and growth factors, such as PDGF, TGF, IGF, and EGF [69]. Another purpose is blood clot formation, which may act as a scaffold [51]. Most of the available data indicated that intracanal bleeding plays a key role in pulp–dentin complex repair [127], however, some studies have demonstrated that cases with the tissue laceration step omitted had successful outcomes as well [127,128]. Palma et al. [129] showed that using blood clotting in the treatment protocol resulted in improved healing outcomes, formation of dentin in the root canal, and also vascularized tissue. Optimally, the top of the blood clot should reach 2–3 mm underneath the cementoenamel junction (CEJ) [130]. Once this is accomplished, a mineral trioxide aggregate (MTA) cement is placed over the blood clot or scaffold to seal the root canal space, and prevent bacterial invasion [83]. MTA exhibits a bioinductive capacity, reparative properties [131], and biocompatibility to tooth tissues [103,132]. An interesting result was provided by research aimed at evaluating histologically the newly generated tissue after RET. The study demonstrated MTA's ability for apical closure induction and resolution of periapical lesions in immature teeth [129]. Nevertheless, MTA is considered to have a potential for discoloration of coronal dentine, when used as a canal sealer [132–134]. This brings a major esthetic concern for anterior teeth treatment. Alternatives to MTA, such as Biodentine can be used to avoid the risk of this negative outcome [135–137]. According to the American Association of Endodontists, to achieve a good coronal seal, a 3–4 mm layer of glass-ionomer should cover the MTA, followed by bonded resin restoration [53]. In fact, it is worth mentioning that recent research revealed a higher shear bond strength value between calcium silicate-based cement (such as Biodentine and MTA) overlaid with resin-based composite than glass ionomer [138–141]. According to Meraji et al. [140], placing the glass ionomer cement over the capping material is not recommended.

Long-term follow-up studies are required to establish reliable outcomes the success rate of regenerative endodontic procedures [51], however, there are no standardized recall protocols [49]. A complete follow-up should include a radiographic and clinical examination. The periapical radiographs allow verifying the increase of root length and width of root walls, and also the resolution of an apical radiolucency [48,142]. The clinical examination should record a positive response to the pulp vitality test, no pain for percussion/palpation, and normal soft tissue appearance [53]. Practicable time-intervals for follow-ups are at 3, 6, 12, 18, and 24 months [49]. Bose et al. advocated that in order to evaluate radiographic evidence of root development there is a need of at least a 12- to 18-month follow-up [143].

Nevertheless, several limitations should be borne in mind when interpreting the results of the present review. First, the search was conducted only in two databases (PubMed and Cochrane Library), thus it could not reveal all available papers associated with regenerative endodontics. The second limitation concerns the choice of the type of analyzed articles. This review focused on clinical cases, which differed in the approach to the patient, choice of method of treatment protocol, time-interval for follow-ups, and the accuracy of the description of the results. Much information was unspecified, or omitted in some articles. That made it impossible to analyze numerous data in detail, such as the etiology of the pulp necrose, root wall thickening and apex closure, and the number of teeth with esthetic problems before and after treatment. Nonetheless, the purpose of our study was focused on different approaches to regenerative endodontic treatment, to provide a summary of the various clinical techniques conducted in dental offices. These limitations may be overcome in future studies by including randomized prospective, retrospective studies or outcome studies, searched for in more databases.

5. Conclusions

The presented data in this review showed that the pulp revascularization procedure may bring a favorable outcome, however, the prognosis of RET is unpredictable. The majority of the studies on regenerative endodontic treatment were performed in teeth with uncompleted root development. The review of the literature shows that infected immature permanent teeth may have a greater potential to achieve a positive result with endodontic treatment than mature teeth, nevertheless, mature teeth also revealed healing processes and became asymptomatic. In the presented clinical cases, the authors adopted various clinical techniques, but they had a common goal of eliminating periapical tissue inflammation and restoring the pulp–dentin complex. Generally, the treatment protocol for regenerative endodontics included minimal or no mechanical instrumentation, canal irrigation with NaOCl, triple antibiotic paste (TAP) as an intracanal medication, and MTA as capping material. Further controlled clinical studies are required to fully understand the process of dentin–pulp complex repair, and the predictability of the procedure.

Author Contributions: Conceptualization, T.S.; methodology, A.M.K., T.S.; formal analysis, A.M.K., K.S.-M., and T.S.; investigation, A.M.K.; resources, A.M.K., T.S.; writing—original draft preparation, A.M.K.; writing—review and editing, A.M.K., K.S.-M., and T.S.; visualization, T.S.; supervision, K.S.-M., and T.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Langer, R.; Vacanti, J.P. Tissue engineering. *Science* **1993**, *260*, 920–926. [CrossRef]
2. Parveen, S.; Krishnakumar, K.; Sahoo, S.K. New era in health care: Tissue engineering. *J. Stem Cells Regen. Med.* **2006**, *1*, 8–24. [PubMed]
3. Capparè, P.; Tetè, G.; Sberna, M.T.; Panina-Bordignon, P. The Emerging Role of Stem Cells in Regenerative Dentistry. *Curr. Gene Ther.* **2020**, *20*, 259–268. [CrossRef] [PubMed]
4. Rao, M.S. Stem Sense: A Proposal for the Classification of Stem Cells. *Stem Cells Dev.* **2004**, *13*, 452–455. [CrossRef] [PubMed]
5. Potdar, P.D. Human dental pulp stem cells: Applications in future regenerative medicine. *World J. Stem Cells* **2015**, *7*, 839–851. [CrossRef] [PubMed]
6. Shi, S.; Gronthos, S. Perivascular Niche of Postnatal Mesenchymal Stem Cells in Human Bone Marrow and Dental Pulp. *J. Bone Miner. Res.* **2003**, *18*, 696–704. [CrossRef] [PubMed]
7. Sangappa, S.K.; Javanaiahar, N.; Kumar, A.P.; Shruti, S. Regenerative endodontic: Current progress. *IOSR J. Dent. Med. Sci.* **2014**, *13*, 88–95. [CrossRef]

8. Ledesma-Martínez, E.; Mendoza-Núñez, V.M.; Santiago-Osorio, E. Mesenchymal Stem Cells Derived from Dental Pulp: A Review. *Stem Cells Int.* **2016**, *2016*, 1–12. [CrossRef]
9. Kawashima, N. Characterisation of dental pulp stem cells: A new horizon for tissue regeneration? *Arch. Oral Biol.* **2012**, *57*, 1439–1458. [CrossRef] [PubMed]
10. Chandki, R.; Kala, M.; Banthia, P.; Banthia, R. From Stem to Roots: Tissue engineering in Endodontics. *J. Clin. Exp. Dent.* **2012**, *4*, e66–e71. [CrossRef]
11. Gong, T.; Heng, B.C.; Lo, E.C.M.; Zhang, C. Current Advance and Future Prospects of Tissue Engineering Approach to Dentin/Pulp Regenerative Therapy. *Stem Cells Int.* **2016**, *2016*, 1–13. [CrossRef]
12. Sonoyama, W.; Liu, Y.; Yamaza, T.; Tuan, R.S.; Wang, S.; Shi, S.; Huang, G.T.-J. Characterization of the Apical Papilla and Its Residing Stem Cells from Human Immature Permanent Teeth: A Pilot Study. *J. Endod.* **2008**, *34*, 166–171. [CrossRef]
13. Kim, S.; Shin, S.-J.; Song, Y.; Kim, E. In Vivo Experiments with Dental Pulp Stem Cells for Pulp-Dentin Complex Regeneration. *Mediat. Inflamm.* **2015**, *2015*, 1–6. [CrossRef]
14. Yu, J.; He, H.; Tang, C.; Zhang, G.; Li, Y.; Wang, R.; Shi, J.; Jin, Y. Differentiation potential of STRO-1+ dental pulp stem cells changes during cell passaging. *BMC Cell Biol.* **2010**, *11*, 32. [CrossRef]
15. Miura, M.; Gronthos, S.; Zhao, M.; Lu, B.; Fisher, L.W.; Robey, P.G.; Shi, S. SHED: Stem cells from human exfoliated deciduous teeth. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 5807–5812. [CrossRef] [PubMed]
16. Nakamura, S.; Yamada, Y.; Katagiri, W.; Sugito, T.; Ito, K.; Ueda, M. Stem Cell Proliferation Pathways Comparison between Human Exfoliated Deciduous Teeth and Dental Pulp Stem Cells by Gene Expression Profile from Promising Dental Pulp. *J. Endod.* **2009**, *35*, 1536–1542. [CrossRef]
17. Sonoyama, W.; Liu, Y.; Fang, D.; Yamaza, T.; Seo, B.-M.; Zhang, C.; Liu, H.; Gronthos, S.; Wang, C.-Y.; Shi, S.; et al. Mesenchymal Stem Cell-Mediated Functional Tooth Regeneration in Swine. *PLoS ONE* **2006**, *1*, e79. [CrossRef]
18. Kaushik, S.N.; Kim, B.; Walma, A.M.C.; Choi, S.C.; Wu, H.; Mao, J.J.; Jun, H.-W.; Cheon, K. Biomimetic microenvironments for regenerative endodontics. *Biomater. Res.* **2016**, *20*, 1–12. [CrossRef] [PubMed]
19. Bakopoulou, A.; Leyhausen, G.; Volk, J.; Tsiftsoglou, A.; Garefis, P.; Koidis, P.; Geurtsen, W. Comparative analysis of in vitro osteo/odontogenic differentiation potential of human dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAP). *Arch. Oral Biol.* **2011**, *56*, 709–721. [CrossRef]
20. Chueh, L.-H.; Huang, G.T.-J. Immature Teeth with Periradicular Periodontitis or Abscess Undergoing Apexogenesis: A Paradigm Shift. *J. Endod.* **2006**, *32*, 1205–1213. [CrossRef]
21. Banchs, F.; Trope, M. Revascularization of Immature Permanent Teeth with Apical Periodontitis: New Treatment Protocol? *J. Endod.* **2004**, *30*, 196–200. [CrossRef] [PubMed]
22. Nagatomo, K.; Komaki, M.; Sekiya, I.; Sakaguchi, Y.; Noguchi, K.; Oda, S.; Muneta, T.; Ishikawa, I. Stem cell properties of human periodontal ligament cells. *J. Periodontal Res.* **2006**, *41*, 303–310. [CrossRef]
23. Seo, B.-M.; Miura, M.; Gronthos, S.; Bartold, P.M.; Batouli, S.; Brahim, J.; Young, M.; Robey, P.G.; Wang, C.Y.; Shi, S. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* **2004**, *364*, 149–155. [CrossRef]
24. Hasegawa, M.; Yamato, M.; Kikuchi, A.; Okano, T.; Ishikawa, I. Human Periodontal Ligament Cell Sheets Can Regenerate Periodontal Ligament Tissue in an Athymic Rat Model. *Tissue Eng.* **2005**, *11*, 469–478. [CrossRef]
25. Bojic, S.; Volarevic, V.; Ljujic, B.; Stojkovic, M. Dental stem cells—Characteristics and potential. *Histol. Histopathol.* **2014**, *29*, 699–706. [CrossRef]
26. Kémoun, P.; Laurencin-Dalicieux, S.; Rue, J.; Farges, J.-C.; Gennero, I.; Conte-Auriol, F.; Briand-Mesange, F.; Gadelorge, M.; Arzate, H.; Narayanan, A.S.; et al. Human dental follicle cells acquire cementoblast features under stimulation by BMP-2/-7 and enamel matrix derivatives (EMD) in vitro. *Cell Tissue Res.* **2007**, *329*, 283–294. [CrossRef]
27. Ahmed, G.M.; Abouauf, E.A.; Abubakr, N.; Dörfer, C.E.; El-Sayed, K.F. Tissue Engineering Approaches for Enamel, Dentin, and Pulp Regeneration: An Update. *Stem Cells Int.* **2020**, *2020*, 5734539. [CrossRef]
28. Kim, S.G.; Zhou, J.; Solomon, C.; Zheng, Y.; Suzuki, T.; Chen, M.; Song, S.; Jiang, N.; Cho, S.; Mao, J.J. Effects of Growth Factors on Dental Stem/Progenitor Cells. *Dent. Clin. N. Am.* **2012**, *56*, 563–575. [CrossRef]
29. Pakyari, M.; Farrokhi, A.; Maharlooei, M.K.; Ghahary, A. Critical Role of Transforming Growth Factor Beta in Different Phases of Wound Healing. *Adv. Wound Care* **2013**, *2*, 215–224. [CrossRef]
30. Musson, D.S.; McLachlan, J.L.; Sloan, A.J.; Smith, A.J.; Cooper, P.R. Adrenomedullin is expressed during rodent dental tissue development and promotes cell growth and mineralization. *Biol. Cell* **2010**, *102*, 145–157. [CrossRef]
31. Zeng, Q.; Nguyen, S.; Zhang, H.; Chebrolu, H.P.; Alzebdeh, D.; Badi, M.A.; Kim, J.R.; Ling, J.; Yang, M. Release of Growth Factors into Root Canal by Irrigations in Regenerative Endodontics. *J. Endod.* **2016**, *42*, 1760–1766. [CrossRef]
32. Malik, Z.; Alexiou, M.; Hallgrímsson, B.; Economides, A.; Luder, H.; Graf, D. Bone Morphogenetic Protein 2 Coordinates Early Tooth Mineralization. *J. Dent. Res.* **2018**, *97*, 835–843. [CrossRef]
33. Aksel, H.; Öztürk, Ş.; Serper, A.; Ulubayram, K. VEGF/BMP-2 loaded three-dimensional model for enhanced angiogenic and odontogenic potential of dental pulp stem cells. *Int. Endod. J.* **2017**, *51*, 420–430. [CrossRef]
34. Yadlapati, M.; Biguetti, C.; Cavalla, F.; Nieves, F.; Bessey, C.; Bohluli, P.; Garlet, G.P.; Letra, A.; Fakhouri, W.D.; Silva, R.M. Characterization of a Vascular Endothelial Growth Factor–loaded Bioresorbable Delivery System for Pulp Regeneration. *J. Endod.* **2017**, *43*, 77–83. [CrossRef] [PubMed]

35. Smith, A.J.; Duncan, H.F.; Diogenes, A.; Simon, S.; Cooper, P.R. Exploiting the Bioactive Properties of the Dentin-Pulp Complex in Regenerative Endodontics. *J. Endod.* **2016**, *42*, 47–56. [CrossRef]
36. Rao, S.M.; Ugale, G.M.; Warad, S.B. Bone Morphogenetic Proteins: Periodontal Regeneration. *N. Am. J. Med. Sci.* **2013**, *5*, 161–168. [CrossRef]
37. Wang, Y.; Li, L.; Zheng, Y.; Yuan, G.; Yang, G.; He, F.; Chen, Y.-P. BMP Activity Is Required for Tooth Development from the Lamina to Bud Stage. *J. Dent. Res.* **2012**, *91*, 690–695. [CrossRef]
38. Saber, S.E.-D. Tissue engineering in endodontics. *J. Oral Sci.* **2009**, *51*, 495–507. [CrossRef]
39. Wang, S.-Z.; Chang, Q.; Lu, J.; Wang, C. Growth factors and platelet-rich plasma: Promising biological strategies for early intervertebral disc degeneration. *Int. Orthop.* **2015**, *39*, 927–934. [CrossRef]
40. Martínez, C.E.; Smith, P.C.; Palma, V. The influence of platelet-derived products on angiogenesis and tissue repair: A concise update. *Front. Physiol.* **2015**, *6*, 290. [CrossRef] [PubMed]
41. Ceccarelli, G.; Presta, R.; Benedetti, L.; De Angelis, M.G.C.; Lupi, S.M.; Baena, R.R.Y. Emerging Perspectives in Scaffold for Tissue Engineering in Oral Surgery. *Stem Cells Int.* **2017**, *2017*, 1–11. [CrossRef]
42. Raghavendra, S.S.; Gathani, K.M. Scaffolds in regenerative endodontics: A review. *Dent. Res. J.* **2016**, *13*, 379–386. [CrossRef]
43. Shah, N.; Logani, A.; Jadhav, G.R. Comparative outcome of revascularization in bilateral, non-vital, immature maxillary anterior teeth supplemented with or without platelet rich plasma: A case series. *J. Conserv. Dent.* **2013**, *16*, 568–572. [CrossRef]
44. Vyas, T. Stem Cell in Modern Dentistry: A Review Article. *Int. J. Res. Health Allied Sci.* **2017**, *3*, 51–59.
45. Albuquerque, M.T.P.; Valera, M.C.; Nakashima, M.; Nör, J.E.; Bottino, M.C. Tissue-engineering-based Strategies for Regenerative Endodontics. *J. Dent. Res.* **2014**, *93*, 1222–1231. [CrossRef]
46. Bottino, M.C.; Pankajakshan, D.; Nör, J.E. Advanced Scaffolds for Dental Pulp and Periodontal Regeneration. *Dent. Clin. N. Am.* **2017**, *61*, 689–711. [CrossRef]
47. Huang, G.T.-J. A paradigm shift in endodontic management of immature teeth: Conservation of stem cells for regeneration. *J. Dent.* **2008**, *36*, 379–386. [CrossRef] [PubMed]
48. Saoud, T.M.A.; Ricucci, D.; Lin, L.M.; Gaengler, P. Regeneration and Repair in Endodontics—A Special Issue of the Regenerative Endodontics—A New Era in Clinical Endodontics. *Dent. J.* **2016**, *4*, 3. [CrossRef]
49. Galler, K. Clinical procedures for revitalization: Current knowledge and considerations. *Int. Endod. J.* **2016**, *49*, 926–936. [CrossRef]
50. Valsan, D.; Pulyodan, M.K.; Mohan, S.P.; Divakar, N.; Moyin, S.; Thayyil, S. Regenerative endodontics: A paradigm shift in clinical endodontics. *J. Pharm. Bioallied Sci.* **2020**, *12*, S20–S26. [CrossRef]
51. Kim, S.G.; Malek, M.; Sigurdsson, A.; Lin, L.M.; Kahler, B. Regenerative endodontics: A comprehensive review. *Int. Endod. J.* **2018**, *51*, 1367–1388. [CrossRef]
52. Galler, K.M.; Krastl, G.; Simon, S.; Van Gorp, G.; Meschi, N.; Vahedi, B.; Lambrechts, P. European Society of Endodontology position statement: Revitalization procedures. *Int. Endod. J.* **2016**, *49*, 717–723. [CrossRef]
53. American Association of Endodontists. *Clinical Considerations for a Regenerative Procedure*; Revised 6-8-16.; American Association of Endodontists: Chicago, IL, USA, 2016.
54. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef] [PubMed]
55. Ajram, J.; Khalil, I.; Gergi, R.; Zogheib, C. Management of an Immature Necrotic Permanent Molar with Apical Periodontitis Treated by Regenerative Endodontic Protocol Using Calcium Hydroxide and MM-MTA: A Case Report with Two Years Follow Up. *Dent. J.* **2019**, *7*, 1. [CrossRef]
56. Xu, Q.; Li, Z. Regenerative Endodontic Treatment of a Maxillary Mature Premolar. *Case Rep. Dent.* **2018**, *2018*, 1–5. [CrossRef]
57. Nagas, E.; Uyanik, M.O.; Cehreli, Z.C. Revitalization of necrotic mature permanent incisors with apical periodontitis: A case report. *Restor. Dent. Endod.* **2018**, *43*, e31. [CrossRef] [PubMed]
58. Žižka, R.; Šedý, J.; Voborná, I. Retreatment of failed revascularization/revitalization of immature permanent tooth—A case report. *J. Clin. Exp. Dent.* **2018**, *10*, e185–e188. [CrossRef]
59. Suresh, N.; Arul, B.; Kowsky, D.; Natanasabapathy, V. Successful Regenerative Endodontic Procedure of a Nonvital Immature Permanent Central Incisor Using Amniotic Membrane as a Novel Scaffold. *Dent. J.* **2018**, *6*, 36. [CrossRef] [PubMed]
60. Samra, R.A.A.; El Backly, R.M.; Aly, H.M.; Nouh, S.R.; Moussa, S.M. Revascularization in Mature Permanent Teeth with Necrotic Pulp and Apical Periodontitis: Case Series. *Alex. Dent. J.* **2018**, *43*, 7–12. [CrossRef]
61. Moodley, D.S.; Peck, C.; Moodley, T.; Patel, N. Management of necrotic pulp of immature permanent incisor tooth: A regenerative endodontic treatment protocol: Case report. *S. Afr. Dent. J.* **2017**, *72*, 122–125.
62. Gürhan, C.; Köseler, İ.; Güneri, P.; Çalışkan, K. Diagnosis and Regenerative Endodontic Treatment of Mandibular Premolar with Type II Dens Invaginatus: A Rare Case Report. *J. Dent. Oral Biol.* **2017**, *2*, 1081.
63. Carmen, L.; Asunción, M.; Beatriz, S.; Rosa, Y.V. Revascularization in Immature Permanent Teeth with Necrotic Pulp and Apical Pathology: Case Series. *Case Rep. Dent.* **2017**, *2017*, 3540159. [CrossRef]
64. Alagl, A.; Bedi, S.; Hassan, K.; Alhumaid, J. Use of platelet-rich plasma for regeneration in non-vital immature permanent teeth: Clinical and cone-beam computed tomography evaluation. *J. Int. Med Res.* **2017**, *45*, 583–593. [CrossRef]
65. Llaquet, M.; Mercadé, M.; Plotino, G. Regenerative endodontic procedures: A review of the literature and a case report of an immature central incisor. *G. Ital. Endod.* **2017**, *31*, 65–72. [CrossRef]

66. Kashikar, R.; Chandak, M.; Mukherjee, P.; Patel, A. Regenerative Endodontic Treatment: A Case Report. *IOSR J. Dent. Med. Sci.* **2017**, *16*, 59–61. [CrossRef]
67. Erkmen Almaz, M.; Akyıldız, M.B.; Şaroglu Sönmez, I. Healing with Incomplete Root Development After Forty Months Fol-lowing: A Case Report. *Meandros Med. Dent. J.* **2017**, *18*, 153–157. [CrossRef]
68. Amitava, B.; Deepashree, P.; Sayani, D.; Ritam, K.; Shabnam, Z.; Gautam Kumar, K. Regenerative pulp therapy for immature non-vital tooth: A case report. *Int. J. Appl. Dent. Sci.* **2016**, *2*, 83–86.
69. Saoud, T.M.; Martin, G.; Chen, Y.-H.M.; Chen, K.-L.; Chen, C.-A.; Songtrakul, K.; Malek, M.; Sigurdsson, A.; Lin, L.M. Treatment of Mature Permanent Teeth with Necrotic Pulps and Apical Periodontitis Using Regenerative Endodontic Procedures: A Case Series. *J. Endod.* **2016**, *42*, 57–65. [CrossRef] [PubMed]
70. She, C.M.L.; Cheung, G.S.P.; Zhang, C. Long-Term Follow-Up of a Revascularized Immature Necrotic Tooth Evaluated by CBCT. *Case Rep. Dent.* **2016**, *2016*, 1–5. [CrossRef]
71. Al-Tammami, M.F.; Al-Nazhan, S.A. Retreatment of failed regenerative endodontic of orthodontically treated immature permanent maxillary central incisor: A case report. *Restor. Dent. Endod.* **2017**, *42*, 65–71. [CrossRef]
72. Subash, D.; Shoba, K.; Aman, S.; Bharkavi, S.K.I. Revitalization of an Immature Permanent Mandibular Molar with a Necrotic Pulp Using Platelet-Rich Fibrin: A Case Report. *J. Clin. Diagn. Res.* **2016**, *10*, ZD21–ZD23. [CrossRef] [PubMed]
73. Aldakak, M.M.N.; Capar, I.D.; Rekab, M.S.; Abboud, S. Single-Visit Pulp Revascularization of a Nonvital Immature Permanent Tooth Using Biodentine. *Iran. Endod. J.* **2016**, *11*, 246–249.
74. Silva, M.H.; Campos, C.N.; Coelho, M.S. Revascularization of an Immature Tooth with Apical Periodontitis Using Calcium Hy-droxide: A 3-year Follow-up. *Open Dent. J.* **2015**, *9*, 482–485. [CrossRef] [PubMed]
75. Guniganti, S.S.; Faizuddin, U.; Solomon, R.V.; Mattapathi, J. Revitalization of traumatized immature tooth with platelet-rich fibrin. *Contemp. Clin. Dent.* **2015**, *6*, 574–576. [CrossRef]
76. Al-Nazhan, S.; Al-Ghamdi, N.S. Pulp revascularization of immature maxillary first premolar. *J. Conserv. Dent.* **2015**, *18*, 496–499. [CrossRef]
77. Miltiadous, M.-E.A.; Floratos, S.G. Regenerative Endodontic Treatment as a Retreatment Option for a Tooth with Open Apex—A Case Report. *Braz. Dent. J.* **2015**, *26*, 552–556. [CrossRef]
78. Chandran, V.; Chacko, V.; Sivadas, G. Management of a Nonvital Young Permanent Tooth by Pulp Revascularization. *Int. J. Clin. Pediatr. Dent.* **2014**, *7*, 213–216. [CrossRef]
79. Aggarwal, G.; Bogra, P.; Singh, S.V.; Gupta, S.; Manchanda, S.; Saini, N. Regeneration of Human Dental Pulp: A Myth or Reality? A Case Report. *Endodontology* **2014**, *26*, 317–322.
80. Kaya-Büyükbayram, I.; Ozalp, S.; Aytugar, E.; Aydemir, S. Regenerative Endodontic Treatment of an Infected Immature Dens Invaginatus with the Aid of Cone-Beam Computed Tomography. *Case Rep. Dent.* **2014**, *2014*, 1–5. [CrossRef]
81. Johns, D.A.; Shivashankar, V.Y.; Krishnamma, S.; Johns, M. Use of photoactivated disinfection and platelet-rich fibrin in regenerative Endodontics. *J. Conserv. Dent.* **2014**, *17*, 487–490. [CrossRef]
82. Güven Polat, G.; Yıldırım, C.; Akgün, O.M.; Altun, C.; Dinçer, D.; Ozkan, C.K. The use of platelet rich plasma in the treatment of immature tooth with periapical lesion: A case report. *Restor. Dent. Endod.* **2014**, *39*, 230–234. [CrossRef] [PubMed]
83. Raju, S.M.K.; Yadav, S.S.; Kumar, S.R.M. Revascularization of Immature Mandibular Premolar with Pulpal Necrosis—A Case Report. *J. Clin. Diagn. Res.* **2014**, *8*, ZD29–ZD31.
84. Forghani, M.; Parisay, I.; Maghsoudlou, A. Apexogenesis and revascularization treatment procedures for two traumatized immature permanent maxillary incisors: A case report. *Restor. Dent. Endod.* **2013**, *38*, 178–181. [CrossRef] [PubMed]
85. Narang, I.; Mittal, N.; Mishra, N. Platelet-rich fibrin-mediated revitalization of immature necrotic tooth. *Contemp. Clin. Dent.* **2013**, *4*, 412–415. [CrossRef] [PubMed]
86. Kim, D.-S.; Park, H.-J.; Yeom, J.-H.; Seo, J.-S.; Ryu, G.-J.; Park, K.-H.; Shin, S.-I.; Kim, S.-Y. Long-term follow-ups of revascularized immature necrotic teeth: Three case reports. *Int. J. Oral Sci.* **2012**, *4*, 109–113. [CrossRef] [PubMed]
87. Aggarwal, V.; Miglani, S.; Singla, M. Conventional apexification and revascularization induced maturogenesis of two non-vital, immature teeth in same patient: 24 months follow up of a case. *J. Conserv. Dent.* **2012**, *15*, 68–72. [CrossRef]
88. Cehreli, Z.C.; Isbitiren, B.; Sara, S.; Erbas, G. Regenerative Endodontic Treatment (Revascularization) of Immature Necrotic Molars Medicated with Calcium Hydroxide: A Case Series. *J. Endod.* **2011**, *37*, 1327–1330. [CrossRef]
89. Thomson, A.; Kahler, B. Regenerative endodontics—Biologically-based treatment for immature permanent teeth: A case report and review of the literature. *Aust. Dent. J.* **2010**, *55*, 446–452. [CrossRef]
90. Petrino, J.A.; Boda, K.K.; Shambarger, S.; Bowles, W.R.; McClanahan, S.B. Challenges in Regenerative Endodontics: A Case Series. *J. Endod.* **2010**, *36*, 536–541. [CrossRef]
91. Levin, L.G. Pulp and Periradicular Testing. *J. Endod.* **2013**, *39* (Suppl. S3), S13–S19. [CrossRef]
92. Palma, P.J.; Martins, J.; Diogo, P.; Sequeira, D.; Ramos, J.C.; Diogenes, A.; Santos, J.M. Does Apical Papilla Survive and Develop in Apical Periodontitis Presence after Regenerative Endodontic Procedures? *Appl. Sci.* **2019**, *9*, 3942. [CrossRef]
93. Mao, T.; Neelakantan, P. Three-dimensional imaging modalities in endodontics. *Imaging Sci. Dent.* **2014**, *44*, 177–183. [CrossRef]
94. Sberna, M.T.; Rizzo, G.; Zacchi, E.; Capparè, P.; Rubinacci, A. A preliminary study of the use of peripheral quantitative computed tomography for investigating root canal anatomy. *Int. Endod. J.* **2009**, *42*, 66–75. [CrossRef]
95. Kim, S.G. Infection and Pulp Regeneration. *Dent. J.* **2016**, *4*, 4. [CrossRef] [PubMed]

96. Murray, P.E.; Garcia-Godoy, F.; Hargreaves, K.M. Regenerative Endodontics: A Review of Current Status and a Call for Action. *J. Endod.* **2007**, *33*, 377–390. [CrossRef] [PubMed]
97. Diogenes, A.; Hargreaves, K.M. Microbial Modulation of Stem Cells and Future Directions in Regenerative Endodontics. *J. Endod.* **2017**, *43*, S95–S101. [CrossRef]
98. Ayoub, S.; Cheayto, A.; Bassam, S.; Najar, M.; Berbéri, A.; Fayyad-Kazan, M. The Effects of Intracanal Irrigants and Medicaments on Dental-Derived Stem Cells Fate in Regenerative Endodontics: An update. *Stem Cell Rev. Rep.* **2020**, *16*, 650–660. [CrossRef]
99. Bezgin, T.; Sönmez, H. Review of current concepts of revascularization/revitalization. *Dent. Traumatol.* **2015**, *31*, 267–273. [CrossRef] [PubMed]
100. Wright, P.P.; Walsh, L.J. Optimizing Antimicrobial Agents in Endodontics. In *Antibacterial Agents*; Kumavath, R., Ed.; IntechOpen: London, UK, 2017. [CrossRef]
101. Elnaggar, S.E.; El Backly, R.M.; Zaazou, A.M.; Elshabrawy, S.M.; Abdallah, A.A. Effect of different irrigation protocols for applications in regenerative endodontics on mechanical properties of root dentin. *Aust. Endod. J.* **2020**. [CrossRef]
102. Martin, D.E.; De Almeida, J.F.A.; Henry, M.A.; Khaing, Z.Z.; Schmidt, C.E.; Teixeira, F.B.; Diogenes, A. Concentration-dependent Effect of Sodium Hypochlorite on Stem Cells of Apical Papilla Survival and Differentiation. *J. Endod.* **2014**, *40*, 51–55. [CrossRef] [PubMed]
103. Kahler, B.; Chugal, N.; Lin, L.M. Alkaline Materials and Regenerative Endodontics: A Review. *Materials* **2017**, *10*, 1389. [CrossRef] [PubMed]
104. Kahler, B.; Lin, L.M. A Review of Regenerative Endodontics: Current Protocols and Future Directions. *J. Istanb. Univ. Fac. Dent.* **2017**, *51* (Suppl. S1), S41–S51. [CrossRef]
105. Aksel, H.; Albanyan, H.; Bosaid, F.; Azim, A.A. Dentin Conditioning Protocol for Regenerative Endodontic Procedures. *J. Endod.* **2020**, *46*, 1099–1104. [CrossRef]
106. Meschi, N.; Hilkens, P.; Van Gorp, G.; Strijbos, O.; Mavridou, A.; Perula, M.C.D.L.; Lambrichts, I.; Verbeken, E.; Lambrechts, P. Regenerative Endodontic Procedures Posttrauma: Immunohistologic Analysis of a Retrospective Series of Failed Cases. *J. Endod.* **2019**, *45*, 427–434. [CrossRef] [PubMed]
107. Kontakiotis, E.G.; Filippatos, C.G.; Tzanetakis, G.N.; Agrafioti, A. Regenerative Endodontic Therapy: A Data Analysis of Clinical Protocols. *J. Endod.* **2015**, *41*, 146–154. [CrossRef]
108. Hameed, M.H.; Gul, M.; Ghafoor, R.; Badar, S.B. Management of Immature Necrotic Permanent Teeth with Regenerative Endodontic Procedures—A Review of Literature. *J. Pak. Med. Assoc.* **2019**, *69*, 1514–1520. [CrossRef] [PubMed]
109. Zhujiang, A.; Kim, S.G. Regenerative Endodontic Treatment of an Immature Necrotic Molar with Arrested Root Development by Using Recombinant Human Platelet-derived Growth Factor: A Case Report. *J. Endod.* **2016**, *42*, 72–75. [CrossRef] [PubMed]
110. Laureys, W.G.; Cuvelier, C.A.; Dermaut, L.R.; De Pauw, G.A. The Critical Apical Diameter to Obtain Regeneration of the Pulp Tissue after Tooth Transplantation, Replantation, or Regenerative Endodontic Treatment. *J. Endod.* **2013**, *39*, 759–763. [CrossRef] [PubMed]
111. Saoud, T.M.A.; Sigurdsson, A.; Rosenberg, P.A.; Lin, L.M.; Ricucci, D. Treatment of a Large Cystlike Inflammatory Periapical Lesion Associated with Mature Necrotic Teeth Using Regenerative Endodontic Therapy. *J. Endod.* **2014**, *40*, 2081–2086. [CrossRef]
112. Paryani, K.; Kim, S.G. Regenerative Endodontic Treatment of Permanent Teeth after Completion of Root Development: A Report of 2 Cases. *J. Endod.* **2013**, *39*, 929–934. [CrossRef]
113. Fang, Y.; Wang, X.; Zhu, J.; Su, C.; Yang, Y.; Meng, L. Influence of Apical Diameter on the Outcome of Regenerative Endodontic Treatment in Teeth with Pulp Necrosis: A Review. *J. Endod.* **2018**, *44*, 414–431. [CrossRef] [PubMed]
114. Mohammadi, Z.; Jafarzadeh, H.; Shalavi, S.; Yaripour, S.; Sharifi, F.; Kinoshita, J.-I. A Review on Triple Antibiotic Paste as a Suitable Material Used in Regenerative Endodontics. *Iran. Endod. J.* **2018**, *13*, 1–6.
115. Kirchhoff, A.L.; Raldi, D.P.; Salles, A.C.; Cunha, R.S.; Mello, I. Tooth discolouration and internal bleaching after the use of triple antibiotic paste. *Int. Endod. J.* **2015**, *48*, 1181–1187. [CrossRef] [PubMed]
116. Thibodeau, B.; Trope, M. Pulp revascularization of a necrotic infected immature permanent tooth: Case report and review of the literature. *Pediatr. Dent.* **2007**, *29*, 47–50.
117. Iwaya, S.-I.; Ikawa, M.; Kubota, M. Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. *Dent. Traumatol.* **2001**, *17*, 185–187. [CrossRef] [PubMed]
118. Chen, M.Y.-H.; Chen, K.-L.; Chen, C.-A.; Tayebaty, F.; Rosenberg, P.A.; Lin, L.M. Responses of immature permanent teeth with infected necrotic pulp tissue and apical periodontitis/abscess to revascularization procedures. *Int. Endod. J.* **2011**, *45*, 294–305. [CrossRef]
119. Ruparel, N.B.; Teixeira, F.B.; Ferraz, C.C.; Diogenes, A. Direct Effect of Intracanal Medicaments on Survival of Stem Cells of the Apical Papilla. *J. Endod.* **2012**, *38*, 1372–1375. [CrossRef]
120. Althumairy, R.I.; Teixeira, F.B.; Diogenes, A. Effect of Dentin Conditioning with Intracanal Medicaments on Survival of Stem Cells of Apical Papilla. *J. Endod.* **2014**, *40*, 521–525. [CrossRef] [PubMed]
121. Tandan, M.; Hegde, M.N.; Hegde, P. Effect of four different intracanal medicaments on the apical seal of the root canal system: A dye extraction study. *Indian J. Dent. Res.* **2014**, *25*, 607. [CrossRef]
122. Kharchi, A.S.; Tagiyeva-Milne, N.; Kanagasingam, S. Regenerative Endodontic Procedures, Disinfectants and Outcomes: A Sys-tematic Review. *Prim. Dent. J.* **2020**, *9*, 65–84. [CrossRef]

123. Andreasen, J.O.; Farik, B.; Munksgaard, E.C. Long-term calcium hydroxide as a root canal dressing may increase risk of root fracture. *Dent. Traumatol.* **2002**, *18*, 134–137. [CrossRef] [PubMed]
124. Kahler, S.L.; Shetty, S.; Andreasen, F.M.; Kahler, B. The Effect of Long-term Dressing with Calcium Hydroxide on the Fracture Susceptibility of Teeth. *J. Endod.* **2018**, *44*, 464–469. [CrossRef] [PubMed]
125. Latham, J.; Fong, H.; Jewett, A.; Johnson, J.D.; Paranjpe, A. Disinfection Efficacy of Current Regenerative Endodontic Protocols in Simulated Necrotic Immature Permanent Teeth. *J. Endod.* **2016**, *42*, 1218–1225. [CrossRef] [PubMed]
126. Chrepa, V.; Henry, M.A.; Daniel, B.J.; Diogenes, A. Delivery of Apical Mesenchymal Stem Cells into Root Canals of Mature Teeth. *J. Dent. Res.* **2015**, *94*, 1653–1659. [CrossRef] [PubMed]
127. Chen, S.-J.; Chen, L.-P. Radiographic outcome of necrotic immature teeth treated with two endodontic techniques: A retrospective analysis. *Biomed. J.* **2016**, *39*, 366–371. [CrossRef]
128. Chueh, L.H.; Ho, Y.C.; Kuo, T.C.; Lai, W.H.; Chen, Y.H.; Chiang, C.P. Regenerative endodontic treatment for necrotic immature permanent teeth. *J. Endod.* **2009**, *35*, 160–164. [CrossRef]
129. Palma, P.J.; Ramos, J.C.; Martins, J.B.; Diogenes, A.; Figueiredo, M.H.; Ferreira, P.; Viegas, C.; Santos, J.M. Histologic Evaluation of Regenerative Endodontic Procedures with the Use of Chitosan Scaffolds in Immature Dog Teeth with Apical Periodontitis. *J. Endod.* **2017**, *43*, 1279–1287. [CrossRef]
130. Estrada, M.M.; Álvarez López, B. Biomateriales tissue engineering and treatment of tooth with apex unripe: Revascularization. *J. Dent. Health Oral Disord. Ther.* **2018**, *9*, 1. [CrossRef]
131. Lourenço Neto, N.; Marques, N.C.; Fernandes, A.P.; Rodini, C.O.; Sakai, V.T.; Abdo, R.C.; Machado, M.A.; Santos, C.F.; Oliveira, T.M. Immunolocalization of dentin matrix protein-1 in human primary teeth treated with different pulp capping materials. *J. Biomed. Mater. Res. B Appl. Biomater.* **2016**, *104*, 165–169. [CrossRef]
132. Staniowski, T.; Brzęcka, D.M. Novel Bioceramic Root Repair Materials: Review of the Literature. *Dent. Med. Probl.* **2016**, *53*, 551–558. [CrossRef]
133. Kahler, B.; Mistry, S.; Moule, A.; Ringsmuth, A.K.; Case, P.; Thomson, A.; Holcombe, T. Revascularization Outcomes: A Prospective Analysis of 16 Consecutive Cases. *J. Endod.* **2014**, *40*, 333–338. [CrossRef] [PubMed]
134. Harlamb, S.C. Management of incompletely developed teeth requiring root canal treatment. *Aust. Dent. J.* **2016**, *61*, 95–106. [CrossRef] [PubMed]
135. Shokouhinejad, N.; Nekoofar, M.H.; Pirmoazen, S.; Shamshiri, A.R.; Dummer, P.M. Evaluation and Comparison of Occurrence of Tooth Discoloration after the Application of Various Calcium Silicate–based Cements: An Ex Vivo Study. *J. Endod.* **2016**, *42*, 140–144. [CrossRef]
136. Yoldaş, S.E.; Bani, M.; Atabek, D.; Bodur, H. Comparison of the Potential Discoloration Effect of Bioaggregate, Biodentine, and White Mineral Trioxide Aggregate on Bovine Teeth: In Vitro Research. *J. Endod.* **2016**, *42*, 1815–1818. [CrossRef] [PubMed]
137. Marconyak, L.J., Jr.; Kirkpatrick, T.C.; Roberts, H.W.; Roberts, M.D.; Aparicio, A.; Himel, V.T.; Sabey, K.A. A Comparison of Coronal Tooth Discoloration Elicited by Various Endodontic Reparative Materials. *J. Endod.* **2016**, *42*, 470–473. [CrossRef]
138. Altunsoy, M.; Tanrıver, M.; Ok, E.; Kucukyilmaz, E. Shear Bond Strength of a Self-adhering Flowable Composite and a Flowable Base Composite to Mineral Trioxide Aggregate, Calcium-enriched Mixture Cement, and Biodentine. *J. Endod.* **2015**, *41*, 1691–1695. [CrossRef]
139. Palma, P.J.; Marques, J.A.; Antunes, M.; Falacho, R.I.; Sequeira, D.B.; Roseiro, L.; Santos, J.M.; Ramos, J.C. Effect of restorative timing on shear bond strength of composite resin/calcium silicate–based cements adhesive interfaces. *Clin. Oral Investig.* **2020**, 1–9. [CrossRef]
140. Meraji, N.; Camilleri, J. Bonding over Dentin Replacement Materials. *J. Endod.* **2017**, *43*, 1343–1349. [CrossRef]
141. Palma, P.J.; Marques, J.A.; Falacho, R.I.; Vinagre, A.; Santos, J.M.; Ramos, J.C. Does Delayed Restoration Improve Shear Bond Strength of Different Restorative Protocols to Calcium Silicate-Based Cements? *Materials* **2018**, *11*, 2216. [CrossRef]
142. Shetty, H.; Shetty, S.; Kakade, A.; Mali, S.; Shetty, A.; Neelakantan, P. Three-dimensional qualitative and quantitative analyses of the effect of periradicular lesions on the outcome of regenerative endodontic procedures: A prospective clinical study. *Clin. Oral Investig.* **2021**, *25*, 691–700. [CrossRef]
143. Bose, R.; Nummikoski, P.; Hargreaves, K. A Retrospective Evaluation of Radiographic Outcomes in Immature Teeth with Necrotic Root Canal Systems Treated With Regenerative Endodontic Procedures. *J. Endod.* **2009**, *35*, 1343–1349. [CrossRef]