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Review Article

Advancing dentin-pulp regeneration: clinical perspectives and insights from stem/progenitor cell transplantation (part II)

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Abstract: This systematic review evaluates clinical studies investigating regenerative endodontic procedures for mature/immature teeth utilizing stem cell transplantation. An electronic search of Scopus, PubMed, ISI Web Science, and Google Scholar was conducted up to January 2023. Outcome measures encompassed radiographic (periapical lesion, root length, apical foramen width, volume of the regenerated pulp) and clinical (post-operative pain, sensibility test) parameters. Among 3250 identified articles, five clinical studies were selected, comprising two randomized controlled trials (RCTs) for mature/immature teeth, and three case reports/series for mature teeth. Despite the promising potential, the included studies exhibited a notable risk of bias. The diversity in stem cells (e.g., dental pulp stem cells [DPSCs], umbilical cord mesenchymal stem cells [UC-MSCs]), scaffolds (Atecollagen, collagen membrane, platelet-poor plasma [PPP], leukocyte platelet-rich in fibrin [L-PRF]), and growth factors (granulocyte colony-stimulating factor [G-CSF]) emphasized the heterogeneity across interventions. In RCTs, DPSCs application increased root length and reduced apical foramen width in immature teeth, while UC-MSCs transplantation reduced apical lesions in mature teeth. Transplantation of DPSCs aggregates or UC-MSCs/PPP also elicited positive pulp responses and increased blood flow. In case reports/series, DPSCs application in teeth with irreversible pulpitis resulted in mineralization and increased the regenerated pulp' volume. Furthermore, transplantation of DPSCs with G-CSF/atelocollagen or L-PRF/collagen membrane led to positive pulp responses. While underscoring the potential of stem cell transplantation for regenerative endodontics in mature/immature teeth, the overall evidence quality and the limited number of available studies emphasize the need for cautious interpretation of results. Future well-designed clinical studies are essential to validate these findings further.

Keywords: Dentin-pulp complex, dental pulp stem cells, regenerative endodontics, stem cell transplantation, systematic review

Introduction

Regenerative endodontics, an interdisciplinary field, employs biologically based approaches for repairing and regenerating the dentin-pulp complex for teeth with necrotic pulps with/without radiographic evidence of periapical pathology. The current strategies in regenerative endodontics predominantly utilize scaffolds, stem cells, and signaling molecules [1, 2]. Numerous clinical and animal studies have concentrated on revitalizing necrotic immature permanent teeth, demonstrating increased dentinal wall thickening and root development by introducing blood into root canal spaces [3-5]. However, histological observations have indicated a lack of dentin-pulp complex formation, with newly grown tissues exhibiting traits similar to cementum, periodontal ligament (PDL), or bone-like tissue [6, 7]. This outcome is hypothesized to be attributed to the absence of stem cells derived from the remaining vital pulp tissue and apical papilla. Essential stem cells for regenerating dentin-pulp tissues may originate from alternative sources such as systemic blood or local tissues like bone and PDL.

Extensive research on the transplantation of stem/progenitor mesenchymal stem cells (MSCs) in clinical trials for cardiovascular dis-

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eases [8] and periodontal regeneration [9, 10] has yielded positive results. These cells exert their effects locally, influencing neovascularization [11], immunomodulation [12], and tissue regeneration [9]. Recent suggestions emphasize the necessity of mesenchymal stem cell transplantation into the root canal for regenerating the dentin-pulp complex.

Our previous systematic review (part I) delved into the effectiveness of stem/progenitor cell therapy in repairing and regenerating the dentine-pulp complex in mature/immature animal teeth. The motivation for the present study is to systematically analyze data from human studies, specifically focusing on the transplantation of stem/progenitor cells to mediate pulp-dentine complex regeneration.

While a previous systematic review assessed the efficacy of stem/progenitor cell transplantation on regenerative endodontics outcomes [13], only one randomized controlled trial (RCT) was included, leaving the evidence inconclusive. New RCTs and case reports/case series have emerged in recent years, evaluating stem/progenitor cell transplantation in regenerative endodontics. Thus, this study systematically reviews clinical studies' data, concentrating on stem/progenitor cell transplantation for pulp-dentin complex regeneration in both mature and immature teeth.

Methods

Protocol

This review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [14]. The guiding PICO question was: "What are the effects of stem/progenitor cell transplantation on the regeneration of the dentin-pulp complex in mature/immature teeth in clinical studies"?

Search strategy

An electronic search encompassing Scopus, PubMed, ISI Web Science, and Google Scholar databases was conducted to identify relevant clinical studies up to January 2023. The search employed keywords such as "Dentin OR odontoblast" AND "regeneration" AND "cell". Grey literature was screened through OpenSigle/OpenGrey, and reference lists of reviews and selected studies were examined for additional studies.

Selection criteria

- Study Design: Case reports, case series, and clinical trials evaluating the stem/progenitor cell transplantation approach in mature or immature teeth requiring regenerative procedures.

- Population: Patients requiring regenerative endodontic procedures.

- Intervention: Stem/progenitor cell transplantation with or without additional treatment involving growth/differentiation factors and/or scaffolds.

- Comparison: No comparison in case reports/case series; standard treatment without stem/progenitor cell transplantation in the control group in RCTs.

- Outcomes: Clinical and radiographical parameters, including sensibility test (thermal test and electrical pulp test [EPT]), post-op pain, pulp blood flow, periapical lesion dimension, apical foramen width, root length, mineralization, and regenerated pulp volume.

Study selection

Titles and abstracts identified in the electronic search underwent independent screening by two reviewers (S.S and A.S) based on the selection criteria. Discrepancies were resolved through discussion, and the selected papers' full texts were subsequently screened.

Data extraction

Two authors (S.S and S.A) independently extracted the following data from the included papers: first author and year of publication, sample size, cell type and concentrations, growth factor(s) used, scaffold/carrier used, clinical protocol, tooth type, pulp/periapical status, and outcomes (radiographic/clinical results).

Risk of bias assessment

- For RCTs, the Cochrane risk of bias tool was followed [15], evaluating domains such as randomization, allocation concealment, blind-

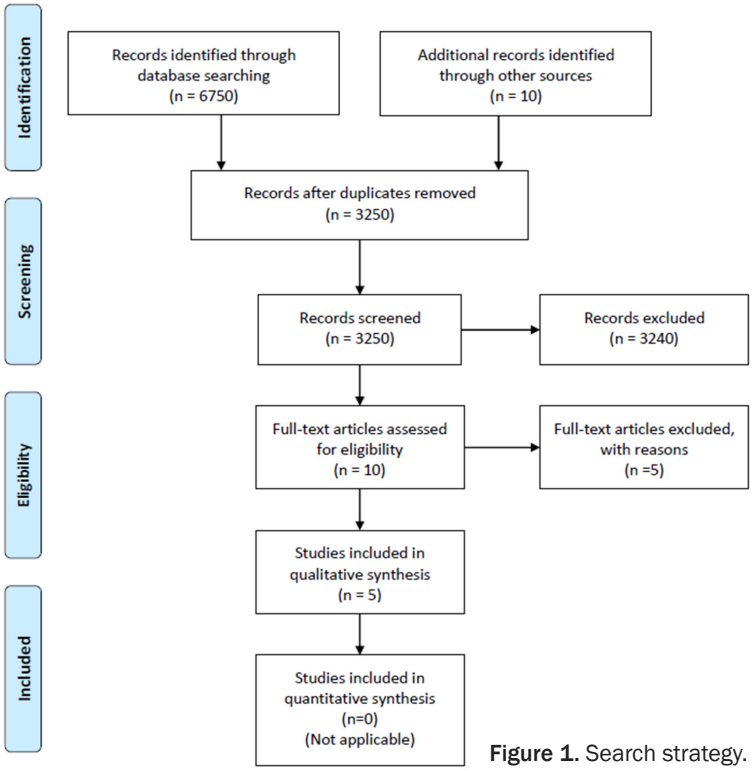

Figure 1. Search strategy.

ing, incomplete outcome data, selective reporting, and other sources of bias.

● Case reports and case series were assessed for methodological quality using the JBI Critical Appraisal Tools [16, 17]. For the case series, the domains evaluated included clear criteria for inclusion, standard and reliable condition measurement, valid methods for participant identification, consecutive inclusion, complete participant inclusion, clear reporting of demographics and clinical information, clear data reporting, and appropriate statistical analysis. For case reports, the same domains were assessed.

Statistical analysis

Statistical analysis was not conducted in this systematic review due to the wide variations in study design, population characteristics, and outcome variables across the included studies. Given the heterogeneity observed among the studies, meta-analysis was not feasible. Instead, the review focused on describing the study characteristics and outcomes of the included studies.

Results

Search results

Figure 1 illustrates the search results and the study selection process. The initial search yielded 3250 papers, and after excluding duplicates and evaluating titles and abstracts, ten records underwent full-text assessment. Finally, five papers were included in the systematic review.

Study characteristics

Table 1 outlines the characteristics of the included studies, spanning from 2017 to 2022. The effects of stem/progenitor cell transplantation on regenerative procedures in mature or immature teeth were assessed in two RCTs, one case series, and two case reports. Routine procedures before cell transplantation included immunocytochemistry, MTT assay, and flow cytometry analyses for characterizing transplanting stem cells.

Study characteristics in RCTs

Two RCTs explored the impact of cell transplantation on regenerative endodontic procedures in necrotic mature or immature teeth [18, 19]. The studies compared the regenerative procedure with apexification in immature teeth [18] or routine endodontic treatment in mature teeth [19]. Autologous dental pulp stem cells (DPSCs) aggregates alone [18] or allogenic umbilical cord-mesenchymal stem cells (UC-MSCs) in combination with platelet-poor plasma (PPP) [19] were used. Radiographic techniques, including periapical and cone beam computed tomography (CBCT), were employed. Clinical assessments included pulp sensibility, pulp blood flow, and post-op pain.

Study characteristics in case reports/case series

One case series [20] and two case reports [21, 22] evaluated the influence of stem cell transplantation on regenerative endodontic proce-

Table 1. Study characteristics of the included studies

	Author (Year)	Groups (n)	Age/sex (F:M)	Teeth	Pulp status	Bleeding	Irrigant/Intracanal	Cell (Concentration)	Scaffold/growth factors	Restoration
RCT	Xuan K (2018)	REP (30), Apexification (10)	7.1/7:33	Immature Incisor	Pulp necrosis	+	3% NaOCl, saline/Metronidazole, Ciprofloxacin, Amoxicillin	Autologous DPSCs aggregate (10×10^7)	-	MTA/GIC
	Brizuela C (2020)	REP (18), Endo (18)	27.5/25:11	Mature Incisors/premolar	Pulp necrosis	+	2.5% NaOCl, saline/Calcium hydroxide	Allogenic UC-MSCs (1×10^6)	PPP encapsulating UC-MSCs	Biodentine/Composite
Case series	Nakashima M (2017)	REP (5)	28.6/2:3	Mature Incisor/premolar	IP	NS	6% NaOCl, 3% H_2O_2, saline/Minocycline or 0.5% Levofloxacin	Autologous mDPSCs (1×10^6)	Atelocollagen encapsulating G-CSF/cell, gelatin sponge over orifices	GIC/Composite
Case-report	Nakashima M (2022)	REP (1)	26/0:1	Mature Molar	IP	NS	Saline, EDTA 3%/TAP	Autologous hpDPSCs (3×10^6)	Atelocollagen encapsulating G-CSF/cell, gelatin sponge over orifices	Biodentine/Composite
	Meza G (2019)	REP (1)	50/0:1	Mature premolar	IP	+	1.5% NaOCl, saline/Calcium hydroxide	Autologous DPSCs (1×10^6)	L-PRF/cell, collagen membrane in coronal part	Biodentine/GIC/Composite

DPSCs, Dental pulp stem cells; Endo, Endodontic treatment; GCSF, Granulocyte-colony stimulating factor; hp-DPSC, Hypoxia treated dental pulp stem cells; H_2O_2, Hydrogen peroxidase; GIC, Glass ionomer cement; L-PRF, Leukocyte platelet-rich fibrin; IP, Irreversible pulpitis; MTA, Mineral trioxide aggregates; mDPSCs, Mobilized dental pulp stem cells; NS, Not stated; NaOCl, Sodium hypochlorite; PPP, Platelet-Poor Plasma; REP, Regenerative endodontic procedure; RCTs, Randomized controlled trials; TAP, Triple antibiotic paste; UC-MSCs, Umbilical cord mesenchymal stem cells.

dures in mature teeth with irreversible pulpitis. Autologous DPSCs [22], autologous mobilized DPSCs [20], or hypoxia-treated DPSCs [21] were used. Different growth factors/scaffolds were employed; two studies used G-CSF in combination with atelocollagen/gelatin sponge [20, 21], while one study used leukocyte-platelet-rich in fibrin (L-PRF) combined with collagen membrane [22]. Radiographic techniques, including periapical, CBCT, and magnetic resonance imaging (MRI), were utilized. Clinical assessments included pulp sensibility and post-op pain.

Risk of bias assessment of the included studies

Table 2 presents the overall quality of the included RCTs using the Cochrane checklist, indicating a low risk of bias. **Tables 3** and **4** present the overall quality of the included studies via the JBI appraisal tool for case series and case reports, respectively, indicating a moderate risk of bias.

*Clinical/radiographic outcomes in RCTs (**Tables 5** and **6**)*

Positive pulp responses were observed with the transplantation of DPSCs aggregates [18], or UC-MSCs/PPP [19]. Notably, both DPSCs aggregates [18] and UC-MSCs/PPP [19] interventions demonstrated an increase in blood flow. Moreover, the application of UC-MSCs/PPP notably resulted in the absence of postoperative pain [19].

Specifically, applying DPSCs led to a significant increase in root length and a concurrent reduction in apical foramen width in immature teeth [18]. Additionally, UC-MSCs transplantation effectively reduced apical lesions in mature teeth [19]. These findings underscore stem cell interventions' diverse positive impacts on both immature and mature teeth, highlighting their potential to enhance regenerative outcomes in endodontic procedures.

*Clinical/radiographic outcomes in case report/case series (**Tables 5** and **6**)*

Positive pulp responses were observed with GCSF-cell-atelocollagen/gelatin sponge with DPSC [21] or mDPSCs [20], and with L-PRF in combination with DPSCs and collagen membrane [22]. No post-op pain was reported with a GCSF-cell-atelocollagen/gelatin sponge with mDPSCs [20]. Mineralized tissue deposition occurred in the apical part with GCSF-atelocollagen/gelatin sponge with DPSCs [21], and L-PRF with DPSCs and collagen membrane [22] resulted in mineralized tissue deposition in the apical and coronal parts. MRI and CBCT evaluations of regenerated pulp volume showed complete pulp regeneration at 24 weeks with GCSF-atelocollagen/gelatin sponge with DPSCs [21] or mDPSCs [20].

Discussion

In the regenerative endodontic procedure, a key element is to manipulate periapical tissue to induce bleeding and form a clot in the apical foramen. However, the unique conditions of mature permanent teeth present challenges compared to immature teeth. Mature teeth have fewer stem cell progenitors and narrower apical foramina, making traditional regenerative procedures difficult [23]. In immature teeth, stem cells from the apical papilla play a significant role in regeneration, as they are located at the apex and can differentiate into functional odontoblastic cells [24, 25]. However, in adults, the apical papilla is absent, and potential stem cells for regeneration come from bone marrow stem cells (BMSCs) and periodontal ligament stem cells (PLSCs) [23]. BMSCs have limitations in regenerating a highly vascularized pulpal volume, while PLSCs tend to differentiate into osteogenic and cementoblastic lineages [26-28]. Moreover, inducing bleeding during pulp revascularization in mature teeth lacks control over the number of stem cells entering the root canal. Donor variability, especially in older patients with lower circulating stem cell concentrations, further complicates treatment outcomes. Variability in MSC markers among patients suggests factors beyond age, sex, and tooth type are at play, potentially related to unknown host factors or the nature and duration of the etiology [29].

A modified regenerative endodontic procedure protocol may be necessary to achieve true dentin-pulp regeneration in mature permanent teeth. Using MSCs from the periapical area, such as personalized cell therapy with autologous DPSCs, could be a viable approach. Human DPSCs possess MSC characteristics, exhibit high proliferation capacity, and have

Table 2. Risk of bias assessment in RCTs

	Randomization	Allocation concealment	Blinding of participants	Blinding of assessors	Incomplete outcome data	Selective reporting	Group similarity	Co-intervention avoided	Lost to Follow-ups	Other risk of bias
Xuan K (2018)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Brizuela C (2020)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No

Table 3. Risk of bias assessment in case-series

	Clear criteria for inclusion	Condition measured in a standard, reliable way	Valid methods used for identification of the participants condition	Consecutive inclusion of participants in case-series	Complete inclusion of participants	Clear reporting of the demographics	Clear reporting of participants' clinical information	Clear reporting of data	Clear reporting of the clinic(s) demographic information	Appropriate statistical analysis
Nakashima M (2017)	Yes	Yes	Yes	?	?	Yes	Yes	Yes	Yes	Yes

Table 4. Risk of bias assessment in case-reports

	Clear description of patient's demographic characteristics	Clear description of patient's history	Clear description of patient's clinical condition	Clear description of diagnostic test or assessment method	Clear description of intervention or treatment procedure	Clear description of post-intervention clinical condition	Clear description of adverse events (harms) or unanticipated events	Does the case report provide takeaway lessons
Nakashima M (2022)	Yes	Yes	Yes	Yes	Yes	NA	No	Yes
Meza G (2019)	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes

Table 5. Clinical outcomes of the included studies

Design	Author (year)	Pulp sensibility			Doppler flowcytometry	Post-op pain
		EPT	Cold test	Hot test		
RCTs	Xuan K (2018)	Decreased sensation in cell therapy (35.29 ± 6.90) and apexification group (0.1 ± 0.17) at 6 m. Decrease in cell therapy (43.43 ± 0.86) and apexification group (0.17 ± 0.16) at 12 m			Increase in cell therapy (6.39 ± 0.83 PU) and decrease in apexification group (0.27 ± 0.58 PU) at 6 m. Increase in cell therapy (7.19 ± 0.77 PU) and decrease in apexification group (0.05 ± 0.48) at 12 m.	
	Brizuela C (2020)	Positive response in the REP group (17% to 50%)	Increasing response in the REP group (6%-56%)	Increasing response in the REP group (0% to 28%)	In the REP group: increase of PU % (60.6%-74.4%) (6 m), and 78.1% (12 m).	Percussion pain (5.6%) in the REP group at 6 m. No percussion pain at 12 m.
Case series	Nakashima M (2017)	Positive response in four patients at 4 w				No post-op pain at 2 w.
	Nakashima M (2022)	Positive response at 1 w				
	13-b	Positive response at 4 w				
	Meza G (2019)	Positive response at 36 w	Delayed response at 36 w			No post-op pain at 36 w.

EPT, Electrical pulp test; REP, Regenerative endodontics procedure; PU, perfusion unit.

Table 6. Radiographic outcomes of the included studies

Design	Author (Year)	Periapical region		Mineralized tissue deposition		Volume of the regenerated pulp		Apical foramen depth (mm)	Root length (mm)
		PA	CBCT	PA	CBCT	MRI	CBCT	CBCT	CBCT
RCTs	Xuan K (2018)							Decrease: cell therapy [6 m: (1.73 ± 0.49), 12 m: (2.64 ± 0.73)], apexification [6 m: (0.44 ± 0.16) and 12 m: (0.62 ± 0.22)]	Increase: cell therapy [6 m: (4.06 ± 0.82), 12 m: (5.24 ± 0.92)], apexification [6 m: (0.61 ± 0.54), 12 m: (0.88 ± 0.67)]
	Brizuela C (2020)	6 and 12 m: no change	Reduction (Endo G [0.35 mm], REP G [0.94 mm])						
Case series	Nakashima M (2017)	24 w: reduced in 4 patients		Obliteration of the enlarged apical portion at 24/28 w (n=3)	Mineralization lateral dentin formation at 28 w (n=3)	Higher SI in the coronal part at 12 w than 24 w. Same SI value as normal pulp, with no difference between the apical/coronal part at 24 w.	Decrease: (from 0.0143 cm^3 to 0.0125 cm^3 and from 0.0110 cm^3 to 0.0081 m^3 in 2 patients) at 28 w.		
Case reports	Nakashima M (2022)	No changes at 48 w	No changes at 48 w	Mineralization in the apical part at 48 w	lateral dentin formation	Complete pulp regeneration at 24 w.	Reduced volume at 24 w.		
		No changes at 48 w	No Lucency		Mineralization at apical third/palatal root at 48 w	Almost similar SI between the affected and control at 24 w.	Decrease the volume at 48 w.		
	Meza G (2019)	Normal	Normal	Mineralization in the middle/apical part					

REP, Regenerative endodontic procedure; PA, Periapical; CBCT, Cone beam computed tomography; MRI, Magnetic resonance imaging.

been successful in animal studies for dental pulp regeneration [25, 30, 31].

In clinical dentistry, determining the status of dental pulp is crucial for effective diagnosis and treatment planning. The most commonly employed methods for this purpose are pulp sensibility tests, specifically the thermal test and EPT [32]. However, these tests rely on subjective responses to external stimuli, providing information on nerve responsiveness rather than directly assessing pulpal vitality [33]. While EPT is useful in confirming the presence of viable tissue in the root canal, it falls short in determining the degree of pulp disease or overall vitality [34]. Moreover, studies still need to demonstrate the utility of the readings or numerical displays obtained through these sensibility tests [35]. In contrast, tests focusing on pulp vitality, such as those measuring pulp blood flow through laser Doppler flow or pulse oximetry, are considered superior in gauging pulp health [36, 37]. Despite their potential advantages, practical challenges must be addressed before these vitality tests become the standard diagnostic tool for evaluating pulp conditions [36]. Pulp sensibility tests can still provide valuable information, especially when combined with additional measures like the use of CO_2 snow or refrigerant spray during EPT [37]. However, this combined approach may have drawbacks, such as a potential false-positive response due to canal moisture [38]. A notable RCT in 2018 explored the regenerative potential of implanting immature necrotic teeth with human DPSC aggregates [18]. The study demonstrated normal blood measurements, elongated roots, and closed apical foramina in incisor teeth, affirming the efficacy of this approach in regenerating functional pulp in young teeth. Another RCT investigated the allogeneic transplantation of PPP encapsulating allogenic UC-MSCs in mature permanent teeth with apical lesions, showing promising results [19]. However, the safety of this approach was evaluated only up to 12 months, and the trials were limited by low sample size and a short follow-up period. Future well-designed RCTs with larger participant numbers, including groups undergoing regenerative endodontic procedures without stem cell transplantation, will be essential to further assess and validate these findings.

In recent developments, MRI has emerged as an alternative radiographic technique for evaluating the volume of regenerated pulp tissue [39]. MRI offers high-resolution images that enable precise differentiation between blood-filled structures of the dental pulp and the adjacent tooth [40]. This imaging modality particularly effectively displays soft tissue abnormalities resulting from inflammation induced by increased water content [41, 42]. However, incorporating the routine use of the MRI technique into daily clinical practice appears to be impractical. Despite its diagnostic benefits, logistical constraints and resource considerations may hinder its widespread adoption in routine dental settings.

Chen et al. reported that subcutaneous transplantation of a cell sheet composed of DPSCs and PRF granules led to pulp-like and dentin-like tissue regeneration within eight weeks [43]. In contrast, another study demonstrated that the transplantation of DPSCs, PRP, or a combination of DPSCs/PRP resulted in the formation of PDL-like, bone-like, or cementum-like tissues in the dogs' teeth [44]. In our current review, we observed a positive response in both the cold test and EPT following the application of DPSCs/L-PRF. Additionally, CBCT images revealed mineralization in the middle and apical thirds of the root canal. G-CSF served as a growth and migration factor in this clinical study, benefitting from approval by regulatory agencies such as the Pharmaceuticals and Medical Devices Agency, Japan (PMDA), the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) [45], with only a few well-described side effects. Moreover, in experimental animal models, the combined local application therapy of G-CSF with MSCs demonstrated promise in enhancing spinal cord regeneration [46] and peripheral nerve regeneration [46]. Nevertheless, histological examination through animal studies is imperative to validate such results.

A potential constraint of this approach lies in its limited feasibility for widespread translation into daily clinical practice, primarily due to the elevated cost associated with autologous therapy and the necessity for adherence to rigorous laboratory practices during its development. Despite these challenges, the favorable outcomes, encompassing both patient and clini-

cian perspectives, underscore the emergence of this clinical protocol as a novel alternative therapy for comparable clinical cases. Substantiating the promising effects of utilizing autologous DPSCs in regenerative endodontic procedures for mature permanent teeth necessitates future randomized controlled studies.

Last but not least, based on this systematic review, it is evident that future research in regenerative endodontics needs to prioritize several key aspects to advance the field. Firstly, well-designed RCTs with larger sample sizes and more extended follow-up periods are urgently required to provide robust evidence on the efficacy and safety of stem/progenitor cell transplantation. To ensure the reproducibility/comparability of results across studies, standardized protocols for cell isolation, characterization, and transplantation techniques should be employed. Additionally, future investigations should focus on identifying optimal sources of stem cells, scaffolds, and growth factors to promote dentin-pulp complex regeneration in mature/immature teeth. Long-term studies assessing the durability and stability of regenerated tissues are also crucial to determine the longevity of treatment outcomes and inform clinical practice.

Conclusion

The present systematic review of clinical studies underscores the potential of stem/progenitor transplantation as a promising therapeutic approach for achieving functional dentin-pulp regeneration. While the evidence level remains low, the findings provide valuable insights. In RCTs focusing on necrotic teeth, applying autologous DPSCs or allogenic UC-MSCs demonstrated favorable radiologic and clinical outcomes in immature and mature teeth, respectively. Case reports and case series revealed that applying autologous DPSCs to teeth with irreversible pulpitis resulted in mineralization and increased volume of the regenerated pulp. However, the low evidence level necessitates cautious interpretation, emphasizing the need for more well-designed RCTs with larger sample sizes to validate these conclusions.

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Disclosure of conflict of interest

None.

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