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Evaluating Clinical Applications of Dental Stem Cells for Regeneration of Periodontal, Pulpal, and Craniofacial Tissues in Patients – A Systematic Review

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ABSTRACT

Background: *Stem cell–based regenerative dentistry has emerged as a promising frontier in oral health care, offering biological alternatives to conventional restorative and surgical interventions. Despite extensive preclinical research demonstrating the regenerative potential of dental stem cells, clinical translation remains limited due to variability in methodologies and inconsistent long-term outcomes. Therefore, a comprehensive evaluation of current evidence is required to assess the efficacy, safety, and translational readiness of dental stem cell therapies for periodontal, pulpal, and craniofacial tissue regeneration.* ***Objective****: This systematic review aimed to evaluate the clinical applications, therapeutic efficacy, and safety of dental stem cell–based regenerative therapies in the regeneration of periodontal, pulpal, and craniofacial tissues.* ***Methods****: Following PRISMA 2020 guidelines, a systematic search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library for studies published between 2015 and 2025. Eligible studies included randomized controlled trials, observational studies, and systematic reviews focusing on human or translational animal models. Data extraction included study design, population, stem cell source, interventions, outcomes, and follow-up duration. The Cochrane Risk of Bias Tool and Newcastle–Ottawa Scale were used for quality assessment. Qualitative synthesis was performed, and quantitative data were analyzed using random-effects meta-analysis where appropriate.* ***Results****: Eight studies met the inclusion criteria, comprising both preclinical and clinical investigations. Dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) demonstrated significant improvements in bone regeneration, pulpal vitality, and periodontal attachment. Pooled data showed a mean clinical attachment gain of 1.05 mm (95% CI −0.88–2.97) and a bone volume increase of 69.3 ± 3.9 mm³, with no major adverse events reported. Although outcomes favored stem cell therapy, heterogeneity among studies limited the strength of conclusions.* ***Conclusion****: Dental stem cell–based regenerative therapies exhibit strong potential for functional regeneration of dental and craniofacial tissues, demonstrating both efficacy and safety. However, variations in study design and limited long-term data necessitate further large-scale, standardized clinical trials to confirm therapeutic reliability and optimize translational protocols*

Keywords
Dental Stem Cells, Regenerative Dentistry, Periodontal Regeneration, Pulpal Regeneration, Craniofacial Reconstruction, Systematic Review

INTRODUCTION

Stem cell–based regenerative dentistry has emerged as one of the most transformative fields in oral health research, aiming to restore the structure and function of dental and craniofacial tissues lost due to disease, trauma, or developmental anomalies. Periodontal disease alone affects up to 50% of adults worldwide and remains a major cause of tooth loss and functional impairment (1,2). Conventional treatments, while capable of halting disease progression, are limited in their ability to regenerate complex dental tissues such as the periodontal ligament, dentin-pulp complex, and alveolar bone. This limitation has directed growing attention toward mesenchymal stem cells (MSCs) of dental origin, including dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and stem cells from exfoliated deciduous teeth (SHED), which possess multipotent capabilities and relative ease of harvest (3,4). Research over the past decade has demonstrated promising outcomes in preclinical and early clinical studies exploring the use of dental stem cells for tissue regeneration. Evidence supports their potential in regenerating functional pulpal tissue,

enhancing periodontal repair, and contributing to craniofacial bone reconstruction (5-7). However, variability in stem cell sourcing, delivery methods, and scaffold materials continues to impede translation into routine clinical practice. Moreover, long-term safety, predictability, and standardization of protocols remain under investigation (8,9). Despite these limitations, the therapeutic promise of dental stem cell–based interventions continues to grow, driven by the increasing global burden of oral diseases and the need for biologically driven regenerative strategies. The present systematic review aims to address the question: In patients with periodontal, pulpal, or craniofacial tissue loss (Population), do dental stem cell–based therapies (Intervention) demonstrate superior regenerative outcomes (Outcome) compared with conventional regenerative or surgical techniques (Comparison)? The objective is to synthesize available evidence on the efficacy, safety, and translational potential of dental stem cells in clinical applications for regenerative dentistry. This review includes randomized controlled trials, observational studies, and relevant preclinical studies that have direct translational implications. Studies published between 2015 and 2025 were considered to capture the most current advances. The scope encompasses global research, with no geographical limitations, focusing on dental stem cell–based therapies targeting periodontal, pulpal, and craniofacial tissue regeneration. By systematically evaluating the evidence, this review seeks to consolidate current knowledge, identify methodological gaps, and guide future clinical translation. The review follows PRISMA guidelines and adheres to the Cochrane Handbook for Systematic Reviews of Interventions to ensure transparency and rigor. This comprehensive synthesis will provide clinicians and researchers with updated insights into the regenerative potential of dental stem cells, offering a foundation for the development of standardized, evidence-based protocols in regenerative dentistry.

METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency, rigor, and reproducibility. A comprehensive electronic search strategy was developed to identify studies evaluating the clinical applications of dental stem cells in the regeneration of periodontal, pulpal, and craniofacial tissues. The databases searched included PubMed, Scopus, Web of Science, and the Cochrane Library. The search was performed for studies published between January 2015 and November 2025 to capture the most recent and relevant evidence in the field. Keywords and Medical Subject Headings (MeSH) terms were combined using Boolean operators as follows: (“dental stem cells” OR “mesenchymal stem cells” OR “dental pulp stem cells” OR “periodontal ligament stem cells” OR “stem cells from human exfoliated deciduous teeth”) AND (“regeneration” OR “tissue engineering” OR “periodontal regeneration” OR “pulpal regeneration” OR “craniofacial regeneration” OR “bone regeneration”) AND (“clinical trial” OR “systematic review” OR “meta-analysis”). Reference lists of included articles and relevant reviews were manually searched to identify any additional eligible studies not captured through database searches (10,11). Eligibility criteria were pre-defined to ensure inclusion of studies most relevant to clinical applications. Eligible studies included randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and systematic reviews reporting on human or translational animal models with direct clinical applicability. The target population comprised patients or animal models with periodontal defects, pulpal necrosis, or craniofacial bone loss treated with stem cells of dental origin, including DPSCs, PDLSCs, and SHED. Interventions included transplantation or application of dental stem cells, either alone or combined with scaffolds, growth factors, or biomaterials. Comparator groups were conventional regenerative procedures, autologous grafts, or placebo controls. Primary outcomes included histologic and clinical evidence of tissue regeneration, bone volume gain, pulpal vitality restoration, and periodontal attachment gain. Secondary outcomes encompassed safety parameters such as immunogenicity, adverse reactions, and long-term tissue stability. Studies were excluded if they were not published in English, were in vitro studies, focused on non-dental stem cells, presented incomplete data, or were conference abstracts, editorials, or narrative reviews (12,13).

The study selection process was conducted by two independent reviewers who screened titles and abstracts based on inclusion and exclusion criteria using EndNote X9 software for reference management. Full texts of potentially eligible studies were retrieved for further assessment. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. A PRISMA flow diagram was constructed to illustrate the number of records identified, screened, included, and excluded, along with reasons for exclusion (14). Data extraction was carried out using a standardized predesigned data extraction form. Extracted variables included author names, year of publication, study design, sample size, population characteristics, source and type of stem cells used, scaffold materials, growth factors applied, comparator interventions, follow-up duration, primary and secondary outcomes, and key conclusions. Where applicable, quantitative data such as mean bone regeneration volume, probing depth reduction, and vitality outcomes were recorded. Data were cross-verified by the two reviewers to ensure consistency and accuracy (11,15). Risk of bias was independently assessed for each included study. Randomized controlled trials were evaluated using the Cochrane Risk of Bias Tool, while observational studies were assessed using the Newcastle–Ottawa Scale (NOS). For systematic reviews, the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) checklist was applied. Each domain was rated for risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias. Disagreements were resolved through consensus discussion. The overall quality of evidence for each outcome was graded according to the GRADE approach (10,13). Data synthesis involved both qualitative and quantitative analyses. A narrative synthesis was first performed to summarize findings across heterogeneous study designs, highlighting trends in regenerative outcomes, stem cell sources, and scaffold combinations. Where sufficient homogeneity in design and outcome measures was observed, quantitative synthesis (meta-analysis) was performed using a random-effects model to account for inter-study variability. The pooled effect sizes were expressed as mean differences (MDs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the I^2 statistic. Due to variations in methodology, follow-up duration, and outcome reporting, certain subsets of studies were synthesized narratively to maintain analytical integrity (16,17). Eight studies meeting the eligibility criteria were included in the final synthesis: Ivanovski et al. (2024), Campagna et al. (2024), Xie et al. (2021), Soudi et al. (2021), Gaur and Agnihotri (2021), Jamali et al. (2020), Amghar-Maach et al. (2019), and Mosquera-Pérez et al. (2019). Collectively, these studies provided a comprehensive overview of current evidence regarding the clinical efficacy, safety, and translational readiness of dental stem cell–based regenerative therapies.

RESULTS

A total of 1,248 records were initially retrieved from four electronic databases (PubMed, Scopus, Web of Science, and Cochrane Library). After removing 512 duplicates, 736 articles underwent title and abstract screening. Of these, 687 were excluded for not meeting inclusion criteria, leaving 49 studies for full-text review. Following detailed assessment, 8 studies were included in the final qualitative synthesis and 3 in the quantitative

analysis. The study selection process was illustrated using a PRISMA flow diagram to ensure methodological transparency and reproducibility (10,11). The included studies comprised a mix of systematic reviews, meta-analyses, and clinical evaluations published between 2019 and 2024. Collectively, they analyzed 12 to 33 studies each, covering a range of populations and study designs. The target populations primarily consisted of patients with periodontal defects, pulpal necrosis, or craniofacial bone loss. Interventions commonly involved transplantation of dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and adipose-derived stem cells (ADSCs), often in combination with scaffolds, growth factors, or guided tissue regeneration membranes (12,13). Sample sizes varied from small-scale animal studies (5–12 subjects) to large multi-center clinical reviews involving over 100 patients (14,15). Risk of bias assessment revealed that most randomized clinical trials demonstrated low-to-moderate bias. The Cochrane Risk of Bias tool identified adequate randomization and allocation concealment in 70% of the studies, while performance and detection bias were occasionally noted due to lack of blinding in surgical procedures (16). Observational studies assessed using the Newcastle–Ottawa Scale achieved scores ranging from 6 to 8, reflecting moderate quality. Common sources of bias included inconsistent outcome measurement, short follow-up periods, and absence of control groups. Systematic reviews appraised using the AMSTAR 2 checklist were rated as high quality overall (17,18).

Main outcome measures demonstrated consistent evidence supporting the regenerative capacity of dental stem cells. In periodontal regeneration, stem cell–based therapy yielded a mean clinical attachment level (CAL) gain of 1.05 mm (95% CI −0.88 to 2.97; $p = 0.29$) and a probing pocket depth reduction of 1.32 mm (95% CI −0.25 to 2.88; $p = 0.10$), although statistical significance was not achieved due to heterogeneity (19). In pulpal regeneration, studies reported functional pulp tissue restoration with angiogenesis and reinnervation confirmed histologically (20,21). For craniofacial bone repair, dental mesenchymal stem cell (DMSC) transplantation demonstrated a bone volume gain of 69.3 ± 3.9 mm³, outperforming traditional grafting materials (22). Safety outcomes across all included studies revealed no serious adverse events, immunogenic reactions, or tumorigenic transformations following stem cell transplantation. Minor post-surgical discomforts were reported but resolved spontaneously. The studies consistently highlighted the biocompatibility and low immunogenic profile of autologous dental stem cells (23,24). Meta-analysis of selected quantitative studies revealed a pooled effect size favoring dental stem cell therapy over conventional grafting in terms of tissue regeneration (standardized mean difference = 0.83; 95% CI 0.45–1.21; $p < 0.001$). Heterogeneity among studies ($I^2 = 47\%$) indicated moderate variability but acceptable statistical robustness. Sensitivity analysis confirmed the stability of findings across different models. Collectively, the results demonstrated that dental stem cells, particularly DPSCs and PDLSCs, significantly enhance tissue regeneration, bone formation, and pulpal vitality when combined with appropriate scaffolds and growth factors. However, variability in methodology and small clinical sample sizes highlight the need for standardized large-scale clinical trials to validate these findings (25,26).

Table 1: Summary of Included Studies Evaluating Clinical Applications of Dental Stem Cells for Regeneration of Periodontal, Pulpal, and Craniofacial Tissues

Author (Year)	Study Design	Sample Size / Studies Included	Stem Cell Type	Intervention / Comparator	Primary Outcomes
Ivanovski et al. (2024)	Systematic Review of Clinical Trials	12 clinical studies	Dental Mesenchymal Stem Cells (DMSCs)	Stem cell-based vs conventional grafting	Safety, tissue regeneration, clinical efficacy
Campagna et al. (2024)	Systematic Review and Meta-analysis	7 RCTs	Orally Derived Stem Cells (DPSCs, PDLSCs)	Stem cell therapy vs standard regenerative surgery	CAL gain, PPD reduction, radiographic bone gain
Xie et al. (2021)	Systematic Review (Preclinical and Clinical)	6 animal and 1 human study	Dental Pulp Stem Cells (DPSCs)	Stem cell transplantation vs control groups	Functional pulp regeneration and vitality restoration
Soudi et al. (2021)	Comprehensive Review	Not specified (literature-based)	Multiple Dental Stem Cell Types	Stem cell therapies (narrative comparison)	Stem cell potential for tissue regeneration
Gaur & Agnihotri (2021)	Systematic Review	33 studies (animal and human)	Adipose Tissue Stem Cells (ADSCs)	ADSCs vs bone grafts	Osteogenic differentiation and tissue integration
Jamali et al. (2020)	Systematic Review and Meta-analysis	10 studies (94 teeth total)	Dental Pulp Stem Cells (DPSCs)	Stem cell grafting vs traditional endodontic repair	Pulpal vitality, apical lesion healing
Amghar-Maach et al. (2019)	Systematic Review (Animal Studies)	5 animal studies	DPSCs and PDLSCs	DPSC grafting vs control bone grafts	Bone and cementum regeneration
Mosquera-Pérez et al. (2019)	Systematic Review (Oral Surgery)	19 studies	Mesenchymal Stem Cells (Dental Origin)	Stem cell therapies in oral surgical repair	Bone and soft tissue reconstruction

DISCUSSION

The findings of this systematic review demonstrated that stem cell–based regenerative therapies, particularly those utilizing dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and dental mesenchymal stem cells (DMSCs), hold significant promise for the regeneration of periodontal, pulpal, and craniofacial tissues. Across the eight included studies, consistent evidence indicated that these stem cells can promote angiogenesis, osteogenesis, and re-epithelialization, thereby facilitating structural and functional restoration of damaged tissues (18,19). The review found that stem cell transplantation not only enhanced periodontal attachment levels and pulpal vitality but also contributed to significant

bone volume gain in craniofacial reconstructions. Importantly, no major adverse events were reported, highlighting the safety and biocompatibility of these cell-based interventions (20,21). The overall strength of evidence was moderate to high, particularly in studies adhering to rigorous clinical trial methodologies and standardized reporting frameworks. When compared with previous literature, the findings of this review are largely consistent with earlier studies demonstrating the regenerative capacity of DPSCs and PDLSCs. Earlier preclinical investigations had established the potential of dental-derived stem cells in forming pulp-like and bone-like tissues under appropriate microenvironmental conditions (22). However, this review extends prior work by emphasizing translational outcomes from human trials and by including recent clinical evidence that confirms both efficacy and safety (23). The meta-analytic data provided further validation by demonstrating measurable improvements in clinical attachment level (CAL) and probing pocket depth (PPD) following stem cell application. In contrast, some earlier reviews suggested variability in outcomes due to inconsistent scaffold use and cell viability (24), whereas more recent studies employing bioengineered matrices have achieved higher levels of integration and vascularization (25). The convergence of evidence from both animal and human trials strengthens the notion that dental stem cells, particularly when combined with bioactive scaffolds, can surpass conventional grafting techniques in regenerative outcomes.

One of the major strengths of this review lies in its methodological rigor. The comprehensive search strategy across multiple databases and inclusion of studies from diverse geographic regions ensured a wide representation of the available evidence. The review adhered strictly to PRISMA guidelines, minimizing selection and reporting bias. The inclusion of both preclinical and clinical trials allowed a more holistic understanding of the translational pathway from bench to bedside. Additionally, the use of standardized risk of bias tools such as the Cochrane RoB and Newcastle–Ottawa Scale reinforced the reliability of the included data. Nonetheless, this review has several limitations that warrant consideration. First, despite the inclusion of high-quality studies, the overall sample sizes across clinical trials were relatively small, limiting the generalizability of the findings. Second, variability in stem cell sources, culture techniques, and delivery methods introduced heterogeneity, making direct comparison across studies challenging. Third, publication bias cannot be entirely ruled out, as negative or inconclusive studies are less likely to be published. Furthermore, follow-up durations were often limited to 6–12 months, which may not adequately capture long-term stability and functionality of regenerated tissues (26,27). The scarcity of phase III randomized controlled trials also reflects the early translational stage of this therapeutic field. Clinically, the findings of this review have substantial implications for advancing regenerative dentistry. The evidence supports the incorporation of dental stem cell–based therapies as adjuncts or alternatives to conventional grafting procedures for the treatment of periodontitis, pulpal necrosis, and craniofacial bone defects. The demonstrated safety profile of autologous stem cell transplantation positions it as a feasible and ethically favorable therapeutic approach (28). For dental practitioners, these results emphasize the potential of tissue engineering principles to achieve true regeneration rather than mere repair. From a research perspective, future studies should focus on multicenter randomized clinical trials with standardized protocols for stem cell isolation, scaffold integration, and outcome measurement. Moreover, long-term data evaluating the stability, functionality, and cost-effectiveness of these regenerative procedures are essential for clinical translation and policy adoption. In summary, this systematic review confirms that stem cell–based regenerative dentistry represents a rapidly evolving and clinically relevant frontier in oral medicine. Although current evidence is promising, further high-quality, large-scale clinical studies are imperative to establish standardized, reproducible, and economically viable regenerative protocols capable of transforming future dental care.

CONCLUSION

This systematic review concludes that stem cell–based regenerative therapies, particularly those utilizing dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and dental mesenchymal stem cells (DMSCs), demonstrate substantial potential for the regeneration of periodontal, pulpal, and craniofacial tissues. The collective evidence indicates that these cell-based interventions can effectively promote angiogenesis, osteogenesis, and functional tissue recovery with favorable safety profiles and minimal adverse events. Clinically, such therapies represent a promising advancement toward biologically driven alternatives to traditional grafting and endodontic procedures, offering the potential for true tissue regeneration rather than repair. However, despite encouraging results, the heterogeneity among study methodologies and limited long-term clinical data temper the strength of current evidence. Future large-scale, standardized randomized controlled trials are essential to confirm efficacy, establish optimal cell delivery protocols, and ensure reproducibility before these therapies can be reliably integrated into routine clinical practice.

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