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Research Article

Stem Cells in Periodontal Regeneration: A Scoping Review

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Abstract

Background: Periodontitis can lead to progressive and irreversible damage of the periodontium, including gingival recessions, loss of soft tissue attachment, intra-bony defects, and eventually tooth loss. In recent years, stem cell-based therapy has been introduced for periodontal tissue regeneration, but the potential effect of this therapy is still unclear. This scoping review aims to systematically explore and outline the available literature that investigated the potential of stem cells in periodontal regeneration.

Methods: A comprehensive electronic review of the available literature in PubMed, Clinical Trial Registration Site, Web of Science, and Scopus databases was conducted in January 2024 within a time frame starting from January 2014. This scoping review follows the extension of PRISMA-sR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as a guideline and includes all studies that investigated the use of any type of stem cells in periodontal tissue regeneration.

Results: The initial search in databases yielded (1213) articles. The (28) included articles that met the eligibility criteria were (4) registered clinical trials, (19) pre-clinical studies, and (5) published eligible randomized clinical trials (RCTs).

Conclusions: Stem cell-based therapy showed promising results in the field of periodontal regeneration, particularly periodontal ligament stem cells (PDLSCs), but the path from basic research to practical therapeutic use is still ongoing.

Keywords: Periodontal; Oral Diagnosis

Introduction

Periodontitis is a destructive inflammatory disease occurring in response to bacterial biofilms on the tooth surface [1]. Non-surgical biofilm removal alleviates inflammation and the progression of the disease. However, the loss of alveolar bone and destruction of the cementum are irreversible [2]. Subsequently, the reparative tissues that form against the root, which are the epithelial tissue on the root surface, and the fibrous connective tissue that fills the residual bone defects, may be prone to future breakdown and re-occurrence of periodontitis [3].

Based on the current understanding of the molecular and cell biology of periodontal tissue development and healing [1]. A paradigm shift from the simple approach of introducing a filler material into a periodontal bony defect to approaches that adapt the recapitulation of the critical events, including cells and biological factors involved in periodontal wound healing, to achieve the regeneration [4].

Actual periodontal regeneration requires at least four criteria to occur to restore the tissues to their original form, function, and consistency. These include the re-establishment of a functional

epithelial seal and the insertion of new Sharpey's fibers into a reformed acellular matrix on the previously exposed root surface to reproduce both the periodontal ligament and the dental-gingival fiber complex. Furthermore, alveolar bone height must be restored within 2 mm of the cementoenamel junction [5,6]. However, the ''crosstalk'' between the components of the periodontium (cellular and matrix), and the limited inherent regenerative capacity of this tissue, needs to be considered [7].

The oral epithelium has been recognized as the source of junctional epithelium. At the same time, periodontal ligament, bone, and cementum cell populations originate from cells in the periodontal ligament and bone during wound healing. Furthermore, the differentiation of cells during regeneration is regulated by variable extracellular matrix molecules and cytokines that induce selective and non-selective responses in the different cell lineages and their predecessors [1,2].

The endogenous regenerating capability in periodontal tissues has been uncovered through an enormous amount of study to comprehend periodontal wound healing. For years, guided tissue regeneration and biomaterial-based strategies for regenerating new periodontal tissues have been used in clinical settings. However, few reports regarding in vivo studies have demonstrated complete regeneration of periodontal tissue using these strategies, probably due to the complexity of periodontal tissues and wound healing [8].

The periodontal, gingival connective tissue, epithelium, and alveolar bone all have numerous amounts of cell populations with the ability to proliferate, root dentin, and cementum which are avascular and contain few cells [1]. Thus, the hypothesis that the type of cell that initially reached the root surface during wound healing would determine the nature of the new tissue that formed was elaborated for the therapeutic strategy that encouraged the selective repopulation of wounds by bone, gingival connective tissue, or epithelial tissue [9].

Reconstruction of lost periodontal tissue requires the combination of cells, scaffolds, signaling molecules, and a blood supply. A limiting factor in achieving periodontal regeneration is the presence of microbial pathogens that contaminate periodontal wounds and reside on tooth surfaces as plaque-associated biofilms and induce inflammation. The critical elements that promote or limit periodontal tissue regeneration are demonstrated in (Figure 1) [10].

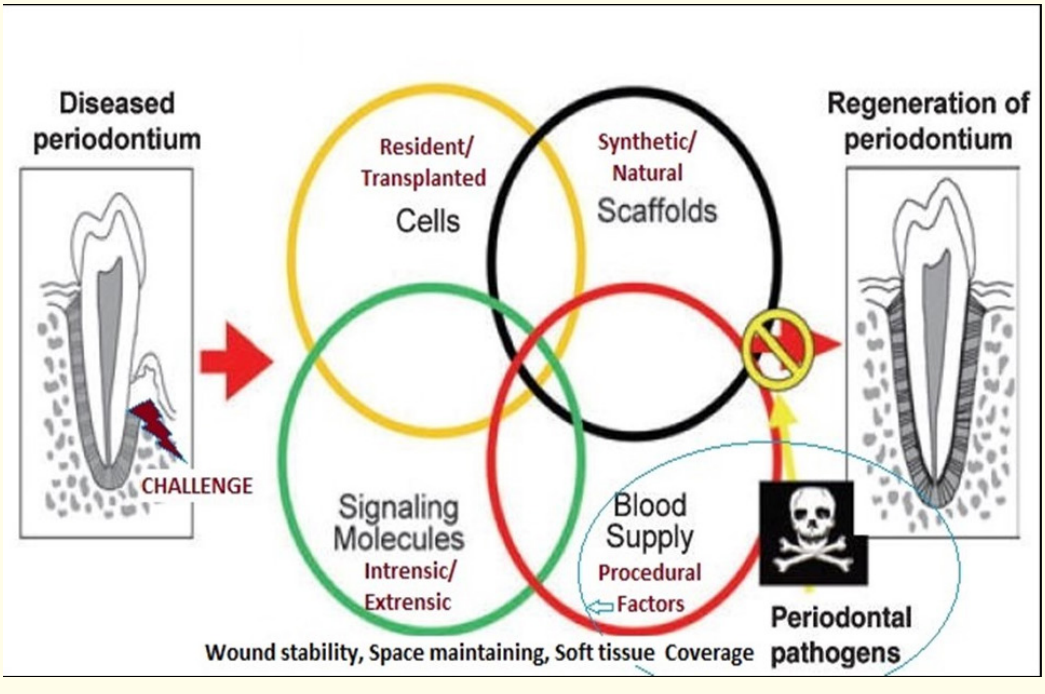

Figure 1: Schematic illustration of essential elements for periodontal tissue regeneration.

The implementation of barrier membranes for space management, clot stabilization, and periodontal tissue repositioning are among the initial strategies that have been adapted to accomplish periodontium regeneration [7]. Later, minimally invasive surgical techniques have shown outstanding outcomes, including lower morbidity and improved patient aesthetics [11]. Recently, periodontal regenerative therapy has progressed significantly, particularly with the advances in biomaterial science and engineering, mostly in the area of multifunctional scaffolding biomaterials [12,13].

Periodontal tissue regeneration approaches aimed at restoring both form and function of healthy periodontium are summarized in (Table 1) [14]. The clinical effectiveness of a variety of periodontal tissue defects was achieved by the current clinical therapy approaches, such as guided tissue/bone regeneration (GTR/GBR) [15]. However, it is still very difficult to accomplish true periodontal regeneration, in terms of the restoration of physiological structure and function through the reformation of the cementum, periodontium, and bone, probably due to a lack of stem/progenitor cells [16].

Category	Details
Bone replacement grafts	Autogenous bone grafts Allografts (freeze dried and demineralized freeze-dried bone) Xenografts Synthetic grafts
Root surface demineralization	Tetracycline , Fibronectin, Enamel matrix proteins
Guided tissue regeneration barriers	Non-resorbable barriers (ePTFE and dPTFE) Resorbable barriers (synthetic polymers, collagen)
Bioactive factors	Growth factors (i.e., PDGF-BB, FGF-2) Differentiation factors (i.e., BMP-2, BMP-7, GDF-5) Enamel matrix derivative Peptides and small molecule drugs Wnt pathway-targeting factors Autologous platelet concentrates
Cell transplantation and recruitment	Oral Derived Mesenchymal Stem Cells Extra-oral Mesenchymal Stem Cells
Combination therapy	*Any two or three of the above*
Tissue-engineered scaffolds	Bio-printed Scaffolds Magnetic Scaffolds

Table 1: Periodontal Tissue Regenerative Approaches.

ePTFE: Expanded Polytetrafluoroethylene; dPTFE: Dense Polytetrafluoroethylene; PDGF: Platelet-Derived Growth Factor; FGF: Fibroblast Growth Factor; BMP: Bone Morphogenetic Protein; GDF: Growth/Differentiation Factor

The regenerative capacity of remaining bone and PDL cells in large periodontal defects and the surface characteristics of periodontitis-affected roots were considered as possible factors limiting these approaches. Moreover, studies showed that defect configuration, surgical factors, and barrier design also played a critical role in determining the extent of periodontal tissue regeneration [17].

The defining features of stem cells that justify their potential effectiveness in regenerative therapy include the capacity to self-renewal and the ability to undergo extensive proliferation, and the potential to reproduce by differentiating into functional cells indicative of several different lineages. In summary, figure 2 demonstrates that stem cells are classified based on their potency into (totipotent, pluripotent, multipotent, oligopotent, and unipotent) and according to their origin or sources into (embryonic, fetal, and perinatal, adult, and induced pluripotent) [18]. Furthermore, the various categories of the differentiation potential of stem cells are outlined in table 2 [18].

The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found. These cells have been identified in many organs and tissues, including the brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, oral and maxillofacial region, heart, gut, liver, ovarian epithelium, and testis. They are thought to reside in a specific area of each tissue *(called a "stem cell niche")*. In many tissues, cur-

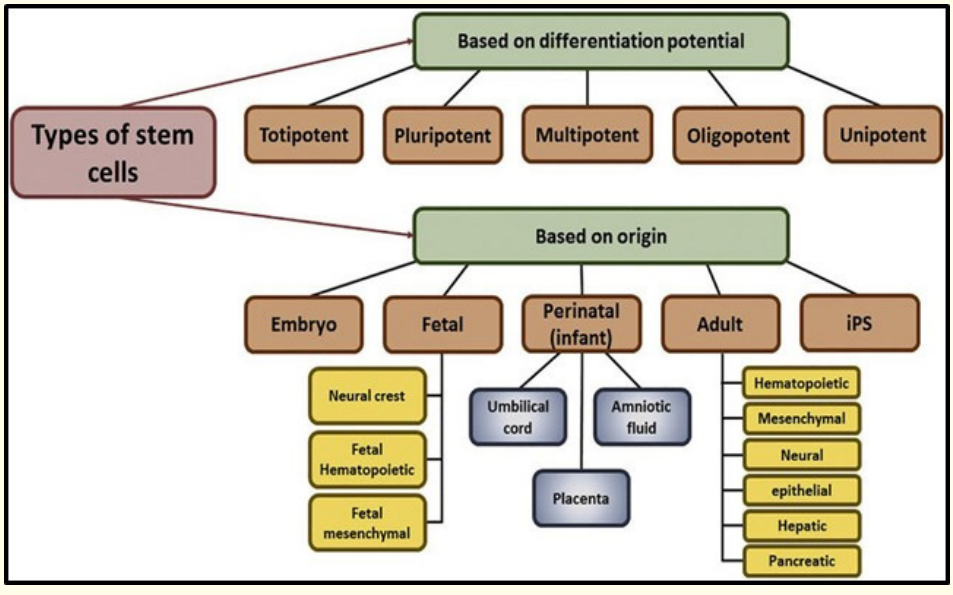

Figure 2: Schematic presentation of stem cell classification according to origin and potency.

Stem Cell Category	Definition	Example
Totipotent	The capacity to differentiate into all possible cell types, including extraembryonic tissues	Fertilized egg
Pluripotent	The ability to differentiate into almost all cell types. Pluripotent cells cannot contribute to extraembryonic tissue and cannot develop into a fetal or an adult animal	Embryonic stem cells
Multipotent	The potential to give rise to cells from multiple, but a limited number of, lineages	Mesenchymal stem cells
Oligopotent	The capacity to differentiate into a few cell types	Myeloid stem cells
Unipotent	The ability to differentiate into only one type of cell	Skin

Table 2: Categories of stem cell potency.

rent evidence suggests that some types of stem cells are pericytes, cells that compose the outermost layer of small blood vessels. Stem cells may remain quiescent (non-dividing) for long periods until they are activated by a normal need for more cells to maintain tissues, or by disease or tissue injury [19].

Growing evidence demonstrates that stem cells are primarily found in niches and that certain tissues contain more stem cells than others. Among these tissues, the dental tissues are considered a rich source of mesenchymal stem cells that are suitable for tissue engineering applications. It is known that these stem cells have the potential to differentiate into several cell types, including odontoblasts, neural progenitors, osteoblasts, chondrocytes, and adipocytes [20]. The multipotency, high proliferation rates, and accessibility make the dental stem cell an attractive source of mesenchymal stem cells for tissue regeneration [21].

There are 13 identified sources of adult stem cells in the oral and maxillofacial region included the following; 1-BMSCs: Bone marrow-derived MSCs from orofacial bone (obtained from bone during drilling of an implant, especially maxilla) 2-DPSCs: Dental pulp stem cells (obtained from de-capping of a vital tooth extracted for orthodontic treatment), 3-SHED: Stem cells from human exfoliated deciduous teeth, 4-PDLSCs: Periodontal ligament stem

cells (obtained by scraping the periodontium of healthy extracted tooth), 5-DFSCs: Dental follicle stem cells (obtained from removal of impacted wisdom at the age of 10 years), 6-TGPCs: tooth germ progenitor cells (it is the core of the tooth germ in impacted wisdom), 7-SCAP: Stem cells from the apical papilla (obtained from removal of impacted wisdom/ at the age of 20 years when two-thirds of the roots are formed), 8-OESCs: Oral epithelial progenitor/stem cells (taken from mucosal epithelium it is totipotent produces only epithelium), 9-GMSCs: Gingiva-derived MSCs (biopsied gingival tissues), 10-PSCs: periosteum-derived stem cells (during opening a partial thickness flap), 11-SGSCs: salivary gland-derived stem cells (Human nonmalignant submandibular SG tissue was obtained from donors), 12-BPFSC: Buccal fat pad stem cells (obtained with simple harvesting from buccal incision), 13- hPCy-MSCs: Human Periapical Cyst-Mesenchymal Stem Cells (obtained from epithelial lining of non-infected radicular cyst) [22,23]. The sources of mesenchymal stem cells in oral and maxillofacial regions are summarized in figure 3.

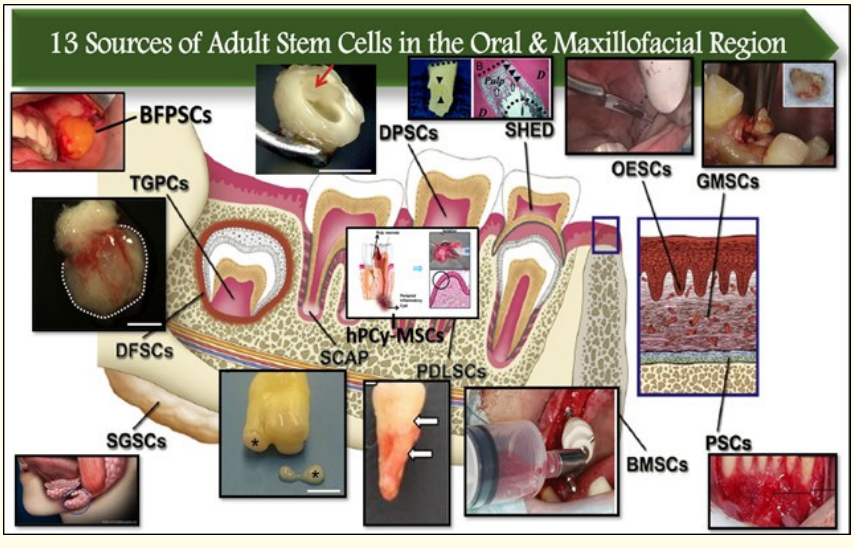

Figure 3: Illustrative figure for various stem cell sources within the oral and maxillofacial region. BMSCs: bone marrow-derived MSCs. DPSCs: dental pulp stem cells. SHED: stem cells from human exfoliated deciduous teeth. PDLSCs: periodontal ligament stem cells. DFSCs: dental follicle stem cells. TGPCs: tooth germ progenitor cells. SCAP: stem cells from the apical papilla. OESCs: oral epithelial progenitor/stem cells. GMSCs: gingiva-derived MSCs. PSCs: periosteum-derived stem cells. SGSCs: salivary gland-derived stem cells. BPFSC: Buccal fat pad stem cells. hPCy-MSCs: human Periapical Cyst-Mesenchymal Stem Cells. (Modified from original reference) [24].

Tissue engineering and cell-based therapies have been introduced as innovative therapeutic techniques to expand the possibilities of regenerative therapy to a wide range of periodontal defects and promote regeneration more predictably. Using the highly proliferative, self-renewing, non-hematopoietic progenitor cells, and mesenchymal stem cells (MSCs), which can differentiate into several mesenchymal cell types, such as osteoblasts and cementoblasts [20].

A wide range of MSCs have been isolated from a variety of tissue sources, such as bone marrow, adipose, perinatal, as well as dental, and oral tissues. particularly autologous cells are most frequently used in recent clinical applications for periodontal tissue regeneration [25-27].

Stem cell acquisition, in vitro expansion, immunogenicity, and ethics are among the limitations of cell therapy in periodontal regeneration which is based on extrinsic cell transplantation. However, naturally endogenous regenerative processes are generally limited and unable to successfully regenerate many tissues. Therefore, current strategies for endogenous regenerative medicine aim to facilitate the recruitment of resident stem cell populations to injured sites by promoting cell mobilization and homing and have become alternative options to cell therapy [16].

Cell aggregates (e.g., cell sheets) retain a large amount of extracellular matrix which can improve cell viability and survival rates after implantation in vivo. Electrostatic spinning and 3D bioprint-

ing through fabricating specific alignments and interactions scaffold structures have made promising outcomes in the construction of a microenvironment conducive to periodontal regeneration. Cell-free therapies with adding biological agents (growth factors, exosomes, and conditioned media) to promote endogenous regeneration, have somewhat addressed the limitations of cell therapy [16,28-34]. Figure 4 represents different strategies for cell-based tissue engineering and cell-free endogenous regeneration for periodontal regeneration [18,34].

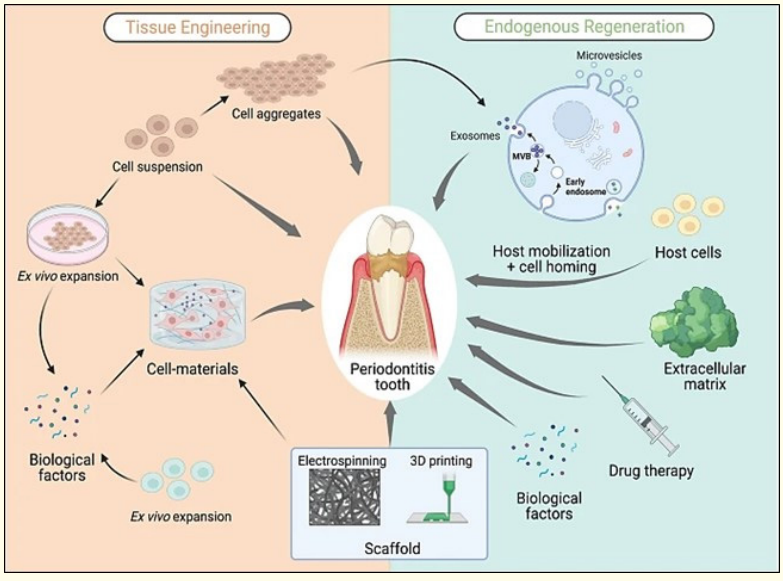

Figure 4: Schematic presentation of stem cell strategies for periodontal regeneration

The available evidence from preclinical studies, including *in vitro*, and *in vivo* research, as well as clinical studies, suggests that stem cells are potentially effective in periodontal regenerative therapy. In this scoping review, these researchers' main results will be systematically outlined, including various types of stem cell strategies applied for different periodontal defects, to explore the current gaps in knowledge and future research perspectives.

Methods

Research guideline

The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews" (PRISMA-ScR) checklist was used as a guideline for this scoping review [35].

Eligibility criteria

All published studies that investigated any type of stem cells in periodontal tissue regeneration within the time frame from January 2014 to January 2024 were considered potentially eligible; no restrictions were applied concerning the design of the study, the type of stem cell applied, the route of delivery, or the scaffold used. Studies in languages other than English were excluded, as well as studies that didn't investigate actual evidence of tissue regeneration as an outcome. Literature reviews were also excluded and used only as sources for bibliographical research.

Research methods and databases

A comprehensive electronic review of the available literature in PubMed, Clinical Trial Registration Site, Web of Science, and Scopus databases was conducted; potentially eligible articles were also searched among references from literature reviews. The keywords and filters applied in the research of these databases were as follows:

- **PubMed:** In [https://pubmed.ncbi.nlm.nih.gov/]. The Filters and keywords applied were [*Keywords (stem cells, periodontal regeneration)- Filters (Clinical Trial, Meta-Analysis, Ran-*

domized Controlled Trial, Review, Systematic Review, from 2014/1/1 - 2024/1/1)]

- **Registered Clinical Trials:** In [https://clinicaltrials.gov/search], using these keywords and filters [*Condition/disease (Periodontal disease), Intervention/treatment (Stem Cells)*]
- **Web of Science:** In [https://www.ekb.eg/web/guest/resources?sourcesLang=en], using [*Stem cells periodontal regeneration and excluding book chapters, editorial materials, and review articles*]
- **Scopus:** In [https://www.scopus.com/search/], applying the following keywords [*stem AND cells, AND periodontal AND regeneration*].

Selection of Sources of Evidence

The search for eligible published articles was conducted according to the pre-specified eligibility criteria, the keywords, and the databases, and then non-eligible publications were excluded and duplications from different databases were filtered and removed using the *Mendeley Reference Manager 2.106.0 (2023 Elsevier Ltd).*

Results

Selection of Sources of Evidence

The database searched produced several bibliographic sources equal to **(**1213 articles). After the removal of duplicates and reviews (1043 articles), (67) potentially eligible articles were obtained, from which only (28) fully met the eligibility criteria and were grouped into (4) registered clinical trials (19) pre-clinical studies which were further classified into those used dental derived stem cells and those used non-dental sources of stem cells or cell-free strategies. There were also (5) published eligible randomized clinical trials (RCTs). The procedure of the identification, selection, and inclusion of the studies is shown in the flowchart of figure 5.

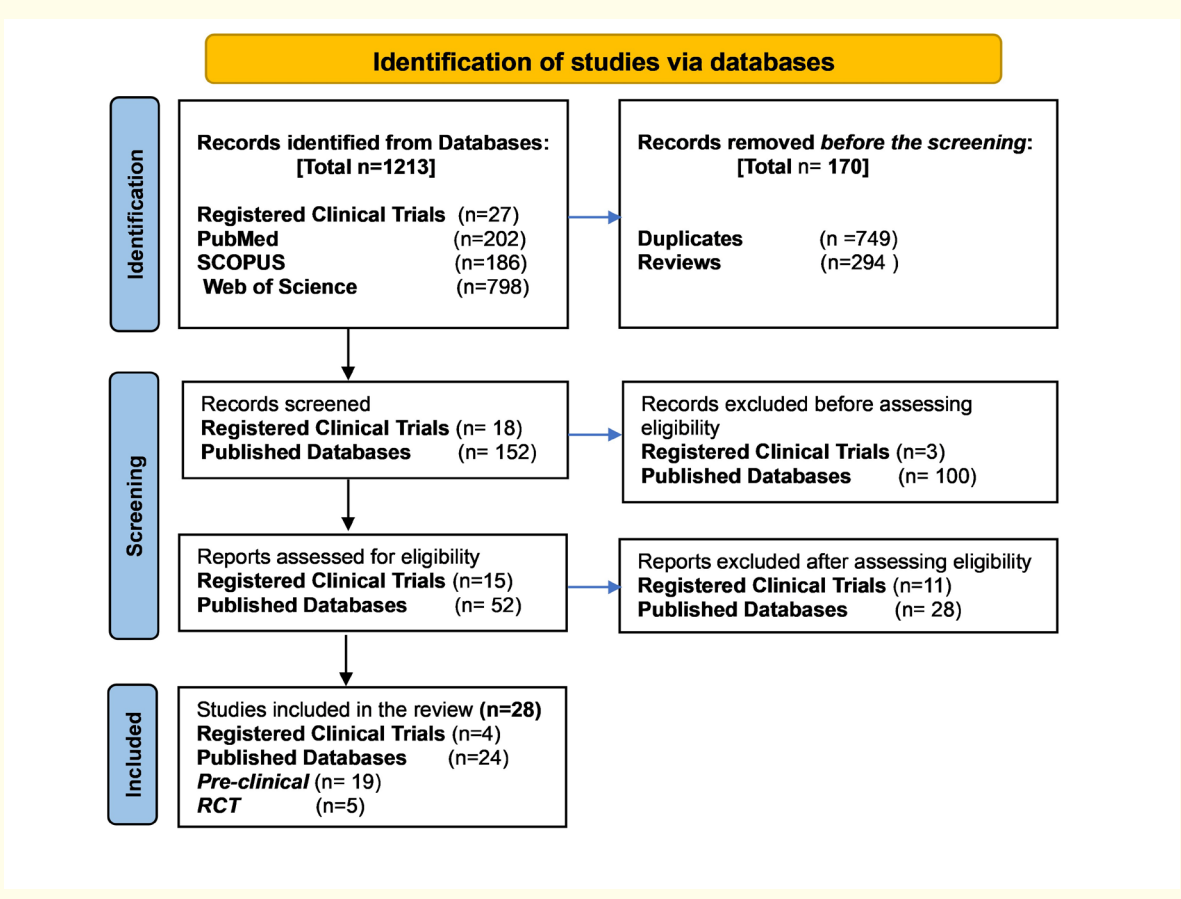

Figure 5: Studies selection and screening procedures as described in the PRISMA flowchart.

Results from clinical trials registry database

Four eligible registered clinical trials for the use of stem cells in periodontal tissue regeneration have been identified between 2014 and 2024 out of (n = 15) trials that were initially found. However, no results have been published from these studies yet in the clinical registry database. Excluded trials were (n = 11) either for using regenerative techniques not related to stem cells (n = 9) or their outcomes were not related to periodontal tissue regeneration but to the safety or tolerability of stem cell injection (n = 2). The basic criteria of the identified eligible trials are summarized in (Table 3).

	NCT Number	Study Title	Periodontal Defect	Type of Stem Cells	Primary Outcome Measured	Number of Participants	First Posted	Locations
1	NCT05924373	Human Dental Pulp Mesenchymal Stem Cells for the Treatment of Chronic Periodontitis Patients	Infra-bony defects	DPSCs	Height of the periodontal bone defect (CBCT) at baseline, 90 days, 180 days	204	2023	China
2	NCT04434794	Treatment of Gingival Recession Using Mesenchymal Stem Cells	Gingival Recession	ADSCs	Number of patients cured month	27	2020	Belarus
3	NCT04270006	Evaluation of Adipose-Derived Stem Cells Exosomes in the Treatment of Periodontitis	Infra-bony defects	ADSCs exosomes	Change in Gingival index (GI), (CAL), Bone level, 0, 3, and 6 months	10	2020	Egypt
4	NCT04297813	Efficacy in Alveolar Bone Regeneration with Autologous MSCs and Biomaterial in Comparison to Autologous Bone Grafting	Alveolar Bone Loss	BMSCs from-Autologous alveolar bone graft	Linear change in bone width baseline-5 months	150	2020	Norway

Table 3: Eligible registered clinical trials for the use of stem cells in periodontal tissue regeneration between 2014-2024.

Results from published database

The data extracted from PubMed, Web of Science, and Scopus databases for the studies published between 2014 and 2024 were screened for duplication and eligibility and the final eligible studies were grouped into pre-clinical and clinical studies. In stem cell transplantation strategy (6) pre-clinical studies used non-dental stem cell transplantation mainly BMSCs and ADMSCs and (8) studies used oral-tissue derived stem cells. Characteristics of the included studies, including the type of stem cells, scaffolds, animal models, and main outcomes, are summarized in tables (Table 4-6). Furthermore, five well-designed randomized clinical trials (RCTs) that used stem cell transplantation strategies for periodontal regeneration were identified and analyzed in (Table 7).

Discussion

Examining the data from pre-clinical investigations, and prior meta-analysis of the results of stem cell-based therapy in periodontal disease showed that stem cells have a positive influence on the development of new bone, cementum, and PDL in periodontal defects [36]. Additionally, other meta-analysis revealed that in pre-clinical investigations using animal models of periodontal defects, PDLSCs and bone marrow mesenchymal stem cells have continuously demonstrated therapeutic advantages on newly produced bone, newly formed cementum, and newly formed periodontal ligament. In the meantime, PDLSCs outperform GMSCs in newly produced cementum and newly formed bone [37].

Dogs, minipigs, sheep, mice, and rats were used as experimental animals, and the periodontal defect morphology was highly variable as well as the scaffolds used; the range of follow-up time was from 4 weeks to 24 weeks.

No published studies compared different types of stem cells or dental with non-dental sources of stem cells applied for periodontal regeneration. However, in a previous meta-analysis for the pre-clinical stem cell-based therapies the results showed that in terms of standardized mean difference (MD) of newly formed bone, PDLSCs was 1.87, BMSCs was 1.88, and DPSCs was 1.69 and were statistically more efficient than scaffold alone. In addition, PDLSCs were superior to GMSCs. For newly formed cementum, PDLSCs (MD) was 2.18, BMSCs was 2.11, and ADSCs was 1.55 and were superior to cell carriers alone. For newly formed periodontal ligaments, PDLSCs (MD) was 1.69 and BMSCs was 1.41 and were more effective than using scaffolds alone, and also PDLSCs were superior

BM-MSC					
Author (Year)	**Animal**	**Scaffold**	**Observation Period**	**Results**	**Regenerated Tissues**
Cai., *et al*. (2015)	Rat	PLGA/ε-caprolactone	6 weeks	Chondrogenic induction of BM-MSC increased periodontal regeneration.	CM, PDL, AB
Nagahara., *et al*. (2015)	Dog	b-TCP/collagen	8 weeks	b-TCP enhanced AB formation by BM-MSC without affecting CM and PDL regeneration.	CM, PDL, AB
Paknejad., *et al*. (2015)	Dog	Bio-Oss® (ABBM)	8 weeks	BM-MSC regenerated more CM and PDL than the scaffold.	CM, PDL
Liu., *et al*. (2016)	Dog	collagen-HA	24 weeks	BM-MSC + collagen/HA induce new CM, PDL, and AB formation.	CM, PDL, AB
ADSC					
Author (Year)	**Animal**	**Scaffold**	**Observation Period**	**Results**	**Regenerated Tissues**
Ozasa., *et al*. (2014)	Dog	Bolheal® (fibrin gel)	6 weeks	ADSC induced new CM, PDL, and AB formation.	CM, PDL, AB
Venkataiah., *et al*. (2019)	Minipig	Bolheal® (fibrin gel)	4 weeks	Allogeneic ADSC regenerated periodontal tissues, comparable to autologous ADSC.	CM, PDL, AB

Table 4: Eligible pre-clinical studies for the use of non-dental stem cells in periodontal tissue regeneration between 2014-2024.

BM-MSC: Bone Marrow-Derived Mesenchymal Stem Cells; ADSC: Adipose-Derived Stem Cells; CM: Cementum; PDL: Periodontal Ligament; AB: Alveolar Bone; HA: Hydroxyapatite; PLGA: Poly(Lactic-Co-Glycolic Acid); b-TCP: Beta-Tricalcium Phosphate; ABBM: Anorganic Bovine Bone Mineral

PDLSC (PDL)					
Author (Year)	**Animal**	**Scaffold**	**Observation Period**	**Results**	**Regenerated Tissues**
Menicanin., *et al*. (2014)	Sheep	Gelfoam	8 weeks	Autologous PDLSC regenerated periodontal tissues with Sharpey's fiber structure.	CM, PDL, AB
Fu., *et al*. (2014)	Minipig	HA/TCP	12 weeks	Allogenic PDLSC and SHED transplantation resulted in periodontal regeneration.	CM, PDL, AB
Han., *et al*. (2014)	Rat	Gelatin sponge	4 weeks	Allogenic PDLSC transplantation resulted in CM, PDL, and AB regeneration at day 21.	CM, PDL, AB
Iwasaki., *et al*. (2014)	Rat	Amniotic membrane	4 weeks	PDLSC on amniotic membrane induced periodontal regeneration.	CM, PDL, AB
Tsumanuma., *et al*. (2016)	Dog	β-TCP, PGA, collagen	8 weeks	CM regeneration was significant in allogenic PDLSC transplantation without side effects.	CM, PDL, AB
Iwasaki., *et al*. (2019)	Rat	Amniotic membrane	4 weeks	Engraftment of transplanted PDLSC was limited in regenerated periodontal tissues.	CM, PDL, AB
DPSC					
Author (Year)	**Animal**	**Scaffold**	**Observation Period**	**Results**	**Regenerated Tissues**
Cao., *et al*. (2015)	Minipig	HA/TCP	12 weeks	DPSC with HGF overexpression induced more periodontal tissues than DPSC.	CM, PDL, AB
SHED					
Fu., *et al*. (2014)	Minipig	HA/TCP	12 weeks	Allogenic PDLSC and SHED transplantation resulted in periodontal regeneration.	CM, PDL, AB

Table 5: Eligible pre-clinical studies for the use of dental stem cells in periodontal tissue regeneration between 2014-2024.

DPSCs: Dental Pulp Stem Cells; SHED: Stem Cells from Human Exfoliated Deciduous Teeth; PDLSCs: Periodontal Ligament Stem Cells; CM: Cementum; PDL: Periodontal Ligament; AB: Alveolar Bone; HA/TCP: Hydroxyapatite and Tricalcium Phosphate; β-TCP: Beta-Tricalcium Phosphate; PGA: Polyglycolic Acid

Author (Year)	Cell Free Treatment	Cell	Animal Model	Results
Nagata., *et al*. (2017)	CM	PDLSC, dermal fibroblasts	rat	PDLSC-CM enhanced periodontal regeneration and inhibited TNF-alpha expression. PDLSC-CM contained various growth factors, angiogenic factors, and cytokines. CM from dermal fibroblasts did not induce regeneration.
Qiu., *et al*. (2020)	CM	PDLSC, GMSC, gingival fibroblasts	rat	CMs from PDLSC and GMSC induced periodontal regeneration. TNF-alpha and IL-1 beta levels were lower in these CM-transplanted sites.
Kawai., *et al*. (2015)	CM	BM-MSC	rat	BM-MSC-CM contained IGF-1, VEGF, and TGF-beta. CM transplantation enhanced periodontal regeneration.
Chew., *et al*. (2019)	Exosome	BM-MSC	rat	Exosomes enhanced the proliferation and migration of PDL cells. Exosome transplantation promoted periodontal tissue healing.
Wu., *et al*. (2017)	Exosome	SHED	rat	SHED-exosome increased angiogenic gene expression in endothelial cells and osteogenesis-related genes in BM-MSC.

Table 6: Eligible pre-clinical studies for the use of stem cell-based cell-free therapy in periodontal tissue regeneration between 2014-2024.

GMSCs: Gingival Mesenchymal Stem Cells; SHED: Stem Cells from Human Exfoliated Deciduous Teeth; PDLSCs: Periodontal Ligament Stem Cells; CM: Conditioned Medium; VEGF: Vascular Endothelial Growth Factor; IGF: Insulin Growth Factor; TGF-Beta: Transforming Growth Factor Beta; TNF: Tumor Necrosis Factor; BM-MSC-CM: Bone Marrow Mesenchymal Stem Cells Conditioned Media; PDLSC-CM: Periodontal Ligament Stem Cells Conditioned Medium

Author (Year)	Cell Type	Sample Size	Experimental Groups	Observation Period	Statistical Significance
Dhote., *et al*. (2015)	Allogenic Cord MSC	14 patients 24 defects	Control: Open flap debridement Test: β-TCP + rhPDGF-BB + cells	6 months	(CAL gain, PPD reduction, radiographic bone fill)
Chen., *et al*. (2016)	Autologous PDLSC	Total: 41 Control: 21 Test: 20	Control: GTR + BioOss Test: GTR + PDLSC + BioOss	3, 6, 12 months	No change in (CAL, PPD, GR)
Ferrarotti., *et al*. (2018)	Autologous DPSC	Total: 29 Control: 14 Test: 15	Control: Collagen sponge Test: Collagen sponge + cells	6, 12 months	(CAL gain, PPD reduction, radiographic bone defect fill)
Sánchez., *et al*. (2020)	Autologous PDL-MSC	Total: 19 Control: 9 Test: 10	Control: Xenogeneic bone substitute Test: Xenogeneic bone substitute + cells	6, 9, 12 months	(Test group showed greater CAL gain and PPD reduction than control, with no statistical significance)
Apatzidou., *et al*. (2021)	Autologous BM-MSC	Total: 27 Each group: 9	Group A: Collagen + fibrin/ platelet lysate + cells Group B: Collagen + fibrin/ platelet lysate Group C: Flap surgery	12 months	(All groups showed similar results)

Table 7: Eligible published randomized clinical studies for the use of stem cells in periodontal tissue regeneration between 2014-2024.

PDSCs: Periodontal Ligament Stem Cells; DPSCs: Dental Pulp Stem Cells; GTR: Guided Tissue Regeneration; PPD: Periodontal Probing Depth; CAL: Clinical Attached Level; GR: Gingival Recession; BM-MSC: Bone Marrow Mesenchymal Stem Cells; PDL-MSC: Periodontal Ligament Stem Cells; β-TCP: Beta-Tricalcium Phosphate.

to GMSCs. Generally, the results of treatment hierarchies demonstrated that the two highest-ranked interventions were PDLSCs and BMSCs [37], and the overall results of these experimental studies validated the use of stem cells in periodontal tissue regeneration.

In the current scoping review, it has been demonstrated, as previously indicated, that stem cell transplantation improved the regeneration of periodontal tissues in several animal models. Thus, proponents of stem cell research urge that now is the moment to translate the research into human clinical trials.

A previously published meta-analysis evaluated the five randomized controlled trials (RCTs) that have been identified in this scoping review which included a total of (118) patients. The results of this meta-analysis demonstrated that stem cell-based therapy showed better statistically significant therapeutic effects on clinical attachment level (CAL) Mean difference (MD) was (-1.18), pocket probing depth (PPD) (MD=−0.75), and linear distance from bone crest to the bottom of the defect (BC-BD) (MD=−0.95) compared with the cell-free groups. However, stem cell-based therapy presented insignificant effects on gingival recession as indicated by the linear distance from the cemento-enamel junction to the bottom of the defect [38].

Interestingly, all of the clinical studies established the safety of stem cell transplantation and stated that clinical parameters such as pocket depth, clinical attachment level, and radiographic bone volume improved by stem cell transplantation. However, only two clinical studies reported statistically significant differences between control and cell treatment. Thus, it was concluded that results from human clinical studies were less impactful than those from preclinical studies and recommended further RCTs with long-term follow-up periods [39]. Unfortunately, these recommendations were not noticed in the registered clinical trials reported in the current scoping review.

Transplanted stem cells are anticipated to locate or migrate, multiply, develop, and generate new tissues at the transplanted site in the majority of stem cell-based tissue regeneration methods. Nonetheless, numerous investigations on cell transplantation have revealed that real transplanted cell engraftment is less likely to occur. This indicates that the regeneration of periodontal tissues by stem cell transplantation may result from accelerated spontaneous wound healing [7,16].

Clinical translation of stem-cell transplantation strategy for periodontal regeneration could be limited by the following: the availability of autologous stem cells in patients with periodontal disease, the possible transmission of infection during ex vivo expansion, and tumor or unintended tissue formation after transplantation. Furthermore, currently, stem cell therapy is considered very expensive compared with regular dental treatments.

Transplantation of a conditioned medium (CM) is a technique that involves harvesting culture supernatant-a secreted substance produced by stem cells-and using it to replace the cells in transplants. Periodontal tissues were shown to regenerate with CM that was derived from PDLSCs [40].

Extracellular vesicles, also known as exosomes, are tiny (less than 100 nm) lipid bilayer-shaped particles that come from cells. Different biological constituents, including proteins, mRNAs, DNA, and miRNAs, are found in exosomes. Since exosomes can be absorbed by far-off cells and perform their functions there, they have lately been identified as new instruments for cell-to-cell communication. Exosomes generated from MSCs are thought to be the source of many of the biological properties that MSCs exhibit, such as immunological control, angiogenesis, anti-inflammation, anti-apoptosis, and modulation of wound healing [41].

It is well recognized that MSC-produced secreted factors have angiogenic, immunoregulatory, anti-inflammatory, and anti-apoptotic properties. Tissue regeneration employing released chemicals or factors from stem cells is being researched as a cell-free treatment for periodontal regeneration in experimental models [28-32].

Cell-free treatment can cover some of the disadvantages of cell transplantation; the possibility of tumor formation and immune rejection is considered below. Furthermore, problems with donor aging and cell sources can be avoided. They can be also stored in freezers, which is more practical, less expensive, and technique-sensitive than cells. However, since tissue regeneration with cell-free treatment improves the patient's wound-healing process, the amount of tissue regeneration may be lower than that with cell transplantation. The number of regenerative studies using cell-free treatment is still small compared with that of cell transplantation, and further extensive research is needed [39].

Conclusion

Wound stability, space preservation, and soft tissue coverage remain important factors, for achieving periodontal regeneration. However, methods that encourage or support residual cells infiltration at the defect periphery may increase the likelihood of new cementum and PDL development. Other strategies, like using biomaterials to replicate mature periodontal structures, implementing several growth factors, delivering cells, or recruiting host cells, have potential but have not always produced consistent outcomes and may not replicate crucial phases of endogenous periodontal wound healing [8,42,43].

Researchers have explored various aspects of tissue engineering in periodontology, including stem cell-based and cell-free therapy that showed promising results in the field of periodontal regeneration, but the path from basic research to practical therapeutic use is still ongoing. Thus, future research prospects should focus on the creation of clinical plans that can enhance, expand, and take advantage of periodontal regeneration's present efficacy.

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