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Next-generation periodontal regeneration: Stem cell–based perspectives

Dr.Vigneshwar Kalyanasundaram Gowri[1], Dr. Pratebha Balu[2], Dr. Saravanakumar ravindran[3], Dr. Akumalla Naga sree[1]

[1] Department of Periodontology, Indira Gandhi institute of dental sciences, Sri Balaji Vidyapeeth, Puducherry, India
[2] Professor, Department of Periodontology, Indira Gandhi institute of dental sciences, Sri Balaji Vidyapeeth, Puducherry, India
[3] Professor, Head of the Department, Department of Periodontology, Indira Gandhi institute of dental sciences, Sri Balaji Vidyapeeth, Puducherry, India

Abstract
Periodontal regeneration remains a major clinical challenge because of the complex, multiphasic architecture of the periodontium (cementum, periodontal ligament, alveolar bone). Stem cell–based strategies (autologous/allogeneic mesenchymal/dental-derived stem cells, cell sheets, cell-free approaches such as secretome/exosomes and cell homing) and they aim to restore structure and function beyond what conventional guided tissue regeneration achieves. Several preclinical studies and an increasing number of randomized clinical trials (RCTs) and meta-analyses report superior improvements in clinical attachment level (CAL), probing pocket depth (PPD) and radiographic bone fill when stem-cell approaches are added to standard therapy, although effect sizes remain modest and study heterogeneity is high. Translation requires consensus on cell source, manufacturing (GMP), scaffold/delivery method, outcome definitions, and regulatory/ethical oversight. This review summarizes current evidence, mechanisms, delivery strategies, safety, limitations, and recommendations for authors preparing manuscripts for publication.

Keywords: Periodontal regeneration, stem cells, dental pulp stem cells, periodontal ligament stem cells, cell sheet, exosomes, clinical trials, meta-analysis

Introduction

Periodontitis affects a large proportion of adults worldwide, and can lead to tooth loss as well as systemic health effects. Conventional regenerative techniques (GTR/GBR, bone grafts, biologics) often fail to fully reconstitute the complex periodontal apparatus. Cell-based regenerative medicine approaches using mesenchymal stem cells (MSCs) or dental-derived stem cells (DPSCs, PDLSCs, SHED, SCAP) offers tissue-specific differentiation, paracrine modulation of inflammation, and capacity to generate multiple periodontal tissues making them attractive therapeutic candidates [1]. Recent systematic reviews and meta-analyses indicate improved clinical outcomes when stem-cell therapies are used adjunctively, but results vary by cell source, scaffold, and study quality.

Stem cell sources used in periodontal regeneration

The overview of different types of stem cells are

Embryonic stem cells (ESCs): The inner cell mass of early-stage embryos is the source of embryonic stem cells (ESCs). They have a special quality called pluripotency, which allows them to differentiate into almost any type of human cell. However, practical and ethical issues, mostly pertaining to the use of human embryos, could enhance their usage in clinical settings, posing serious moral conundrums and disputes.

Adult stem cells: Unlike embryonic stem cells, they are present in a variety of bodily tissues and are essential for tissue upkeep and repair. Mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) are two important adult stem cells in periodontal regeneration. These adult stem cells are a good choice for research and possible therapeutic uses in periodontal regeneration because they are easier to get and less problematic in terms of ethics than ESCs.

Induced pluripotent stem cells: iPSCs be reprogrammed from adult cells, including skin or blood cells, to display characteristics like pluripotency that are comparable to those of embryonic stem cells. With the ability to produce patient-specific stem cell lines, iPSCs offer a way to create individualized regenerative treatments. Although there are less ethical issues with iPSCs than with ESCs, maintaining the safety and effectiveness of iPSC-based treatments is still crucial for their advancement and use in clinical settings [2].

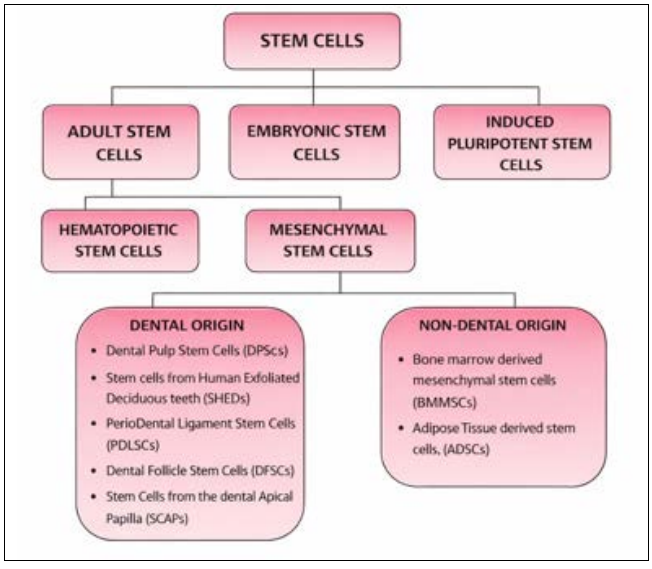

Fig 1: Overview and Classification of Stem Cells in Regenerative Medicine

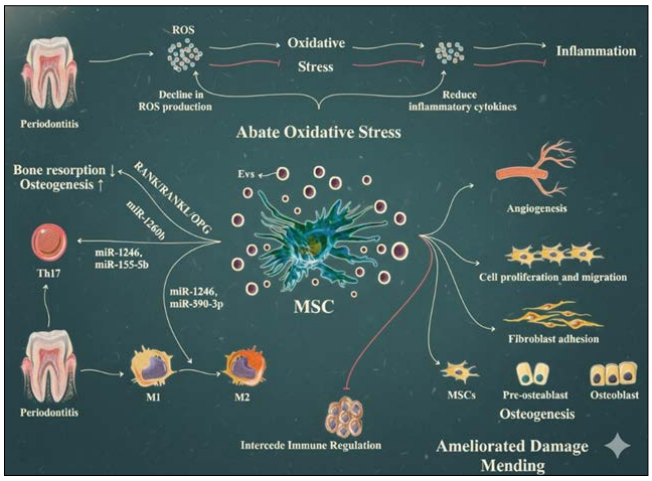

Fig 2: Mesenchymal Stem Cells as Master Regulators of Oxidative Stress, Inflammation, and Periodontal Regeneration

Periodontal ligament stem cells (PDLSCs):

- **Periodontal ligament stem cells (PDLSCs):** These are tissue-specific, able to form cementum-like tissue and oriented PDL fibers in animal models. A promising tool for periodontal regeneration, periodontal ligament stem cells (PDLSCs) are found in the perivascular region of the periodontium and exhibit traits of mesenchymal stem cells. PDLSC transplantation has advanced significantly in recent years. By altering culture conditions and using growth factors, researchers are trying to maximize the potential for PDLSC proliferation and differentiation. However, issues still exist [3].

- **Dental pulp stem cells (DPSCs):** Dental Pulp Stem Cells (DPSCs) are mesenchymal stem cells derived from the dental pulp with strong proliferative capacity, multilineage differentiation potential, and immunomodulatory properties. Functionally, DPSCs contribute to dentin–pulp repair, angiogenesis, neurogenesis, and extracellular matrix regulation. In periodontics, DPSCs play a significant role in regenerative therapy by differentiating into cementoblast-like, osteoblast-like, and fibroblast-like cells, thereby contributing to regeneration of the periodontal ligament, cementum, and alveolar bone. Their paracrine action promotes angiogenesis, modulates inflammation, and enhances wound healing. DPSCs have been successfully applied in preclinical models for periodontal defect regeneration, intrabony defect repair, and bioengineered periodontal constructs, making them one of the most promising stem cell sources for future periodontal therapeutic strategies [4].

- **Dental Follicle Stem Cells (DFSCs):** Dental follicle stem cells (DFSCs) are neural crest–derived cells located around the developing tooth germ. They are multipotent and can differentiate into osteoblasts, cementoblasts, periodontal ligament cells, adipocytes, chondrocytes, and various neuronal and epithelial lineages. Key markers for DFSC identification include CD13, CD44, CD73, CD105, CD271, STRO-1, NOTCH-1, and HLA-ABC, with CD44 and STRO-1 being the most specific [5].

DFSCs play a vital role in periodontium development and demonstrate strong immunomodulatory activity. They reduce pro-inflammatory cytokines such as IL-4, IL-8, and IFN-γ. DFSCs also influence macrophage polarization toward the M2 phenotype, thereby limiting inflammation and bone resorption.

These vesicles promote PDLSC migration, proliferation, and osteogenic differentiation such as reduced immunogenicity, minimal tumor risk, and easier clinical handling. SEVs from dental stem cells also regulate bone remodeling through the OPG/RANKL/RANK signaling pathway, highlighting their promise as a cell-free therapeutic strategy [6].

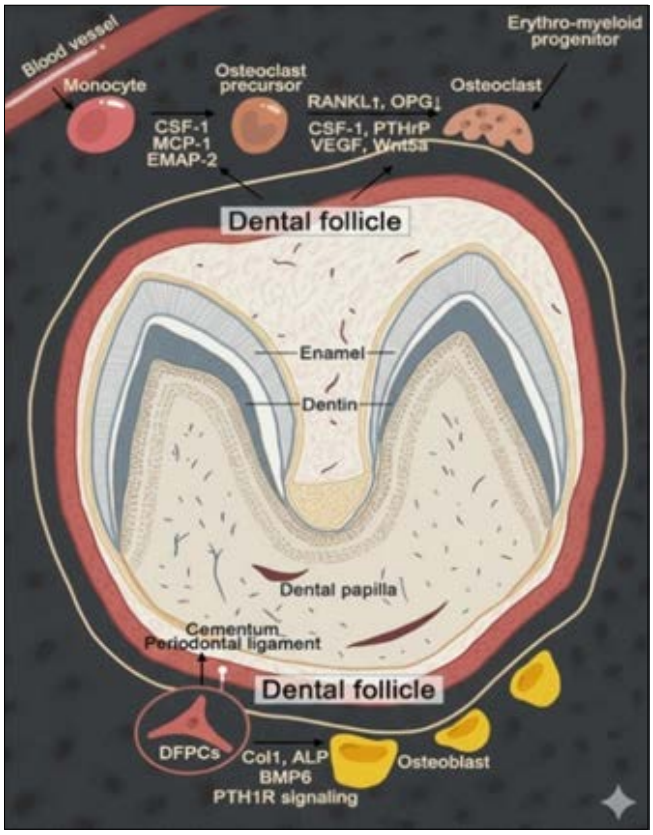

Fig 3: Dental Follicle Stem Cells in Tooth and Periodontal Development

- **Deciduous teeth (SHED), apical papilla (SCAP), gingival mesenchymal stem cells (GMSCs), adipose-derived MSCs, bone marrow (MSCs):** Mesenchymal stem cells isolated from various dental and extra-dental tissues exhibit distinctive biological properties and regenerative capacities, making them highly relevant for periodontal tissue engineering.

- **Stem cells from human exfoliated deciduous teeth (SHED):** SHED represent a highly proliferative and multipotent population derived from exfoliated primary teeth. SHED demonstrate strong osteogenic, neural, and angiogenic potential, surpassing many adult MSCs in proliferation rate. Their ability to induce mineralized tissue formation and secrete potent trophic factors positions them as an attractive candidate for periodontal bone regeneration and modulation of inflammatory periodontal defects [7].

- **Stem cells from the apical papilla (SCAP):** These are isolated from the developing root apex of immature

permanent teeth and display remarkable odontogenic and osteogenic differentiation ability. Biologically, SCAP exhibit higher proliferative and migratory capacities than DPSCs and are enriched in stemness markers such as STRO-1 and CD146. Their unique developmental origin provides them with strong potential in regenerating cementum-like tissue and contributing to the formation of periodontal ligament-like fibers, making them well suited for root-associated periodontal regeneration and bio-root engineering.

- **Gingival mesenchymal stem cells (GMSCs):** Originate from the lamina propria of gingival connective tissue and can be obtained through minimally invasive harvesting. GMSCs exhibit rapid expansion, stable phenotype, and strong immunomodulatory function, including suppression of T-cell responses and reduction of inflammatory cytokines. GMSCs have demonstrated efficacy in promoting soft-tissue healing, reducing periodontal inflammation, and regenerating PDL-like structures when combined with scaffolds or growth factor systems.

- **Induced Pluripotent Stem Cells (iPSCs):** They are a particular kind of pluripotent stem cell that can be produced straight from a somatic cell. They are able to proliferate endlessly and give rise to all other types of cells in the body. Dental cells such as DPSCs, SHEDs, PDLSCs, and SCAPs have recently been effectively converted into iPSCs, and iPCSs have been studied for periodontal regeneration.

- **Dental follicle precursor cells:** DFPCs improves periodontal regeneration by PDLSCs in vivo. DFPCs appear to enhance the self-renewal and multi-differentiation capacity of PDLSCs, which indicates that DFPCs could provide a beneficial microenvironment for periodontal regeneration by using PDLSCs [8]

- **Adipose-derived mesenchymal stem cells (ADSCs):** are easily collected through minimally invasive liposuction procedures and provide a highly abundant, autologous MSC source. ADSCs exhibit multilineage differentiation, including osteogenic, chondrogenic, and angiogenic pathways. The secretion of VEGF, HGF, and anti-inflammatory cytokines supports their role in periodontal wound healing, bone regeneration, and mitigation of chronic periodontal inflammation. ADSCs have been widely studied in scaffold-based approaches for intrabony and furcation defect repair.

Bone marrow-derived MSCs (BMMSCs) remain the classical and most extensively characterized MSC population. They possess robust osteogenic and chondrogenic differentiation potential and widely employed in preclinical models of periodontal regeneration. BMMSCs can generate alveolar bone, cementum-like tissue, and well-organized PDL fibers. Despite the invasive nature of bone marrow aspiration, BMMSCs continue to serve as a "gold-standard" comparison for evaluating other stem cell types due to their proven regenerative efficacy and broad immunomodulatory properties [9].

Table 1: Comparative Overview of Stem Cells Used in Periodontal Regeneration

Stem Cell Type	Source	Tissue Potential	Clinical Feasibility
PDLSCs	Periodontal ligament	Cementum, PDL, bone	High
DPSCs	Dental pulp	Bone, cementum	Moderate
SCAP	Apical papilla	Root dentin, bone	Experimental
DFPCs	Dental follicle	PDL, cementum	Experimental
GMSCs	Gingiva	PDL, bone	High
BMMSCs	Bone marrow	Bone, cementum	High (invasive)
ADSCs	Fat tissue	Bone, soft tissue	High
iPSCs	Reprogrammed somatic cells	All periodontal tissues	Experimental

Mechanisms of Action

Stem cells aid regeneration through the following

1. **Direct differentiation into osteoblasts/cementoblasts/PDL fibroblasts;**

- **Osteogenic differentiation:** One of the main ways stem cells promote periodontal regeneration is through their ability to undergo osteogenic differentiation. Stem cells, particularly MSCs, can differentiate into osteoblasts, the specialized cells responsible for bone formation. The differentiation of stem cells into osteoblasts facilitates the restoration of alveolar bone, contributing to the overall efficacy of periodontal regeneration.

- **PDL cell differentiation:** The ability of stem cells to develop into PDL cells is another crucial component of periodontal regeneration mediated by stem cells. The Periodontal Ligament is a specialized connective tissue that anchors teeth to the alveolar bone, providing stability and shock absorption during mastication. By regenerating PDL cells, stem cell-based therapies aim to improve tooth stability and prevent further tooth mobility, a common consequence of periodontal disease.

- **Cementogenic differentiation:** Certain types of stem cells have the rare capacity to develop into cementoblasts, which are specialized cells that create cementum. Stem cell-based treatments seek to improve the integrity of the tooth-root interface by regenerating cementum, supporting appropriate tooth anchoring and periodontal health. Paracrine secretion that modulate inflammation,

    - **Growth factors and cytokines:** Through the release of growth factors and cytokines, stem cells are essential for the regeneration of periodontal tissue. Bioactive substances include TGF-β, FGF, and VEGF. TGF-β is involved in immune modulation and tissue healing, FGF encourages cell proliferation and tissue repair, while VEGF increases angiogenesis.

- **Extracellular vesicles (EVs):** MicroRNAs, proteins, and other bioactive molecules that are essential for cell-to-cell communication are released by stem cells. With their microRNAs impacting gene expression and processes like differentiation and proliferation, these EVs can modify the behavior of nearby cells in the periodontal microenvironment [2].

2. **Immunomodulation to create a pro-regenerative niche; and Immunomodulatory effects:** MSCs have significant immunomodulatory characteristics that are pertinent to periodontal regeneration. The host immune response to microbial infections frequently results in persistent inflammation in the periodontal microenvironment. MSCs can help control the local immunological environment by reducing this excessive inflammatory response. MSCs improve the environment for tissue regeneration and repair by reducing the immune response [10].

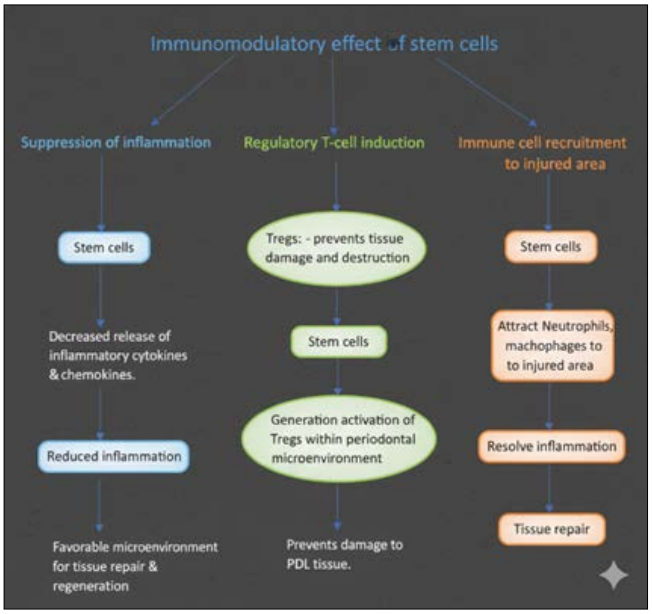

Fig 4: Immunomodulatory Effects Of stem cells

3. **ECM remodeling when delivered as cell sheets. Exosome/secretome therapy reproduces many paracrine benefits without live cells.**

Stem cells paracrine functions aid in controlling the remodeling of the extracellular matrix (ECM) in periodontal tissues. Tissue architecture and function are significantly influenced by the extracellular matrix, which serves as the tissues structural framework. By modulating the activity of cells involved in tissue remodeling, stem cells paracrine functions contribute to the maintenance of a balanced extracellular matrix. The periodontal region's tissue architecture, functioning, and homeostasis are all supported by this control [11].

Periodontal Applications

- **Regeneration of periodontal ligament (PDL):** Periodontal ligament (PDL) regeneration represents a major goal in periodontal regenerative therapy, and the study by Dangaria et al. (2011) provides strong experimental evidence supporting the use of PDL progenitor cells for predictable regeneration. In this work, the authors isolated periodontal progenitor cells and pre-seeded them onto natural tooth root surfaces before implantation [12]. This allowing the cells to attach, proliferate, and differentiate along the root surface. The pre-seeded roots were then implanted into an in vivo model, where the cells demonstrated the ability to generate new periodontal ligament fibers, cementum-like tissue, and organized extracellular matrix key components of a functional PDL apparatus.

- **Cementum regeneration:** Stem-cell–based strategies play a central role in achieving true periodontal regeneration because they provide the biological capacity to rebuild all components of the periodontal attachment apparatus. According to Liu et al. (2019) [13], mesenchymal stem cells (MSCs) from various sources—such as PDLSCs, DPSCs, SCAP, BMMSCs, and GMSCs—can differentiate into cementoblasts, fibroblasts, and osteoblasts, enabling coordinated regeneration of cementum, periodontal ligament, and alveolar bone. These factors modulate inflammation, enhance angiogenesis, and stimulate host repair.

- **Alveolar bone regeneration:** Stem cells play a crucial therapeutic role in periodontal alveolar bone regeneration by providing osteogenic cells capable of rebuilding bone lost due to periodontitis. Hollý et al. (2021) [14], mesenchymal stem cells (MSCs) from dental and extraoral sources—such as PDLSCs, DPSCs, BMMSCs, ADSCs, and SCAP are used for their ability to differentiate into osteoblasts, regenerate mineralized tissue, and enhance bone repair. When delivered with scaffolds or biomaterials it significantly accelerate new bone formation, improve defect fill, and re-establish the structural integrity of the alveolar process [15].

- **Periodontal defect filling:** Periodontal defect filling refers to the use of regenerative materials such as stem cells, scaffolds, and biomaterials to restore tissue lost due to periodontitis. The success of defect filling largely depends on the morphology of the defect, especially whether it is contained (intrabony) or non-contained.

1. Contained defects (3-wall) naturally support the regenerative materials by providing bony walls that help maintain space, stabilize the wound, and enhance vascularization, making defect filling more predictable. These defects allow stem cells and graft materials to remain in place, improving bone formation and PDL regeneration.

2. Non-contained defects, which lack surrounding walls, present difficulties in retaining materials and stabilizing the blood clot. The article notes that advanced strategies such as 3D-printed scaffolds, hydrogels, microspheres, and stem-cell–loaded biomaterials are being developed to improve defect filling in such challenging areas.

3. Stem-cell–based defect filling enhances periodontal regeneration by supplying cells capable of differentiating into osteoblasts, cementoblasts, and PDL fibroblasts, forming all components of the periodontal apparatus.

- **Bioengineered periodontal complex:** Periodontal ligament stem cells (PDLSCs), dental pulp stem cells (DPSCs), and mesenchymal stem cells (MSCs) are commonly used because they can differentiate into ligament fibroblasts, osteoblasts, and cementoblasts, thereby reconstructing multiple tissues simultaneously. Beyond differentiation, these stem cells exert paracrine and immunomodulatory effects, releasing growth factors and cytokines that reduce inflammation, promote blood vessel formation (angiogenesis), and recruit host progenitor cells more favorable in healing process.

Hydrogels loaded with stem cells can be injected into periodontal defects, while 3D bioprinting allows precise placement of cells in a pattern that mimics bone-ligament-cementum interfaces [17].

- **Inflammation Reduction:** Mesenchymal stem cells (MSCs) derived from the periodontal ligament, dental pulp, gingiva, and bone marrow—play a major role in controlling and reducing inflammation in periodontal disease. According to Goriuc et al. (2023), these cells secrete a wide range of anti-inflammatory mediators, such as IL-10, TGF-β, and prostaglandin E2, which actively suppress pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 that are elevated in periodontitis. By altering this cytokine balance, stem cells shift the environment from a destructive, inflammatory state toward a healing-oriented, regenerative state.

This macrophage polarization results in reduced tissue breakdown, improved angiogenesis, and enhanced recruitment of endogenous repair cells. These combined effects, stem cells not only decrease inflammation but also create the ideal biological environment for periodontal regeneration and defect healing [18].

- **Enhanced wound healing:** Xu et al. (2019) highlight that stem cells accelerate periodontal wound healing primarily through their paracrine actions, rather than only through direct differentiation. Periodontal stem cells such as PDLSCs, DPSCs, GMSCs, and BM-MSCs—release a wide range of bioactive molecules, including VEGF, TGF-β, IGF, and anti-inflammatory cytokines. These signals significantly enhance angiogenesis, improve blood supply to the wounded area, and create a biologically favorable environment that speeds up soft-tissue closure and reduces healing time [19].

It modulates the local immune response, reducing excessive inflammation and promoting a transition towards tissue repair and remodeling. They enhance fibroblast activity, stimulate extracellular matrix production, and support organized collagen deposition, which are essential for stable periodontal wound healing. Stem-cell–based such as cell sheets, scaffolds, or conditioned media demonstrate superior wound healing, faster and more predictable periodontal tissue recovery [20].

- Adjunct in guided tissue regeneration (GTR) Ramseier et al. (2012) describe how traditional GTR relies on barrier membranes to exclude epithelial downgrowth and allow periodontal ligament and bone cells to repopulate a defect [21]. The review highlights that stem-cell–based adjuncts significantly enhance the regenerative outcomes of GTR by providing a biologically active source of progenitor cells capable of forming new bone, periodontal ligament, and cementum. When incorporated into GTR systems either delivered on scaffolds, membranes, or as cell sheets—periodontal stem cells (PDLSCs), bone-marrow MSCs, and other dental MSCs offer superior regenerative potential compared to natural wound healing alone.

Stem cells act as bioactive adjuncts by releasing growth factors, promoting angiogenesis, and modulating inflammation at the GTR site, thereby improving the stability of the wound and increasing the likelihood of achieving true periodontal regeneration.

- Potential future use Assir et al. (2016) highlight that future periodontal therapy will increasingly rely on stem-cell–based, biologically driven regeneration[22] rather than conventional surgical repair. The authors emphasize several promising directions: the use of autologous or allogeneic MSCs for predictable regeneration of bone, PDL, and cementum; development of cell sheets and scaffold-free constructs capable of reproducing native periodontal architecture; and incorporation of gene-enhanced stem cells to promote targeted osteogenesis or immunomodulation. They also point to the potential of induced pluripotent stem cells (iPSCs), which could offer unlimited patient-specific regenerative cells. Additionally, advances in 3D bioprinting, exosome-based therapies, and cell-loaded biomaterials may allow precise reconstruction of complex periodontal defects.

Delivery Strategies and Adjuncts in Stem Cell Therapy for Periodontal Regeneration

The successful application of stem cell therapy in periodontal regeneration largely depends on the effective delivery system that ensures cell viability, targeted placement, and sustained activity at the defect site. Various delivery strategies have been explored to optimize stem cell retention and functional integration within periodontal tissues.

1. Scaffold-Based Delivery Systems

Biocompatible scaffolds act as 3D-matrices that support cell adhesion, proliferation, and differentiation. Natural polymers such as collagen, chitosan, gelatin [23], and fibrin have shown favorable properties for periodontal applications due to their biodegradability and similarity to the extracellular matrix (ECM). Synthetic polymers like polylactic acid (PLA) and polycaprolactone (PCL) are also used for controlled degradation and mechanical stability [24, 25]

Composite scaffolds combining stem cells with growth factors (e.g., PDGF, BMP-2, or VEGF) further enhance periodontal ligament and alveolar bone regeneration.

- **Cell suspension + scaffold (e.g., collagen, HA/TCP):** simple but may have poor retention and orientation. Preclinical histology shows bone and PDL-like tissue formation with appropriate scaffolds.

- **Multiphasic/biphasic scaffolds & micropatterning:** guide formation of distinct tissues (bone vs PDL) and improve fiber orientation.

2. Injectable Hydrogels

Injectable hydrogels are gaining popularity as minimally invasive carriers for stem cell delivery. Hydrogels derived from alginate, hyaluronic acid, and gelatin methacrylate (GelMA) provide a hydrated microenvironment conducive to cell survival and differentiation. These systems can be injected directly into intrabony defects, adapting to irregular defect morphology while maintaining localized release of bioactive molecules [26].

3. Cell Sheet Technology

Cell sheet engineering allows the transplantation of intact cell layers with preserved ECM and intercellular connections, eliminating the need for scaffolds. Periodontal ligament stem cell (PDLSC) sheets have demonstrated superior cementum–ligament–bone complex regeneration compared to cell suspensions [27]. Layered cell sheets can be combined with growth factors or membranes to enhance integration and stability.

- **Cell-free approaches (secretome/exosomes) and homing strategies:** harness paracrine effects and avoid cell-manufacturing complexities; emerging data show promise in preclinical studies and early clinical investigations [28].

4. Microcarriers and Nanoparticle Systems

Microcarriers serve as 3D culture substrates for large-scale stem cell expansion and delivery. Microcarriers and nanoparticle-based systems have emerged as advanced biomaterial platforms designed to improve the delivery, survival, and functional activity of stem cells in regenerative dentistry. Microcarriers provide a high surface-area-to-volume ratio that supports extensive cell attachment, proliferation, and three-dimensional expansion of MSCs under dynamic culture conditions. These are fabricated from biocompatible polymers such as gelatin, collagen, PLGA, or chitosan, allow scalable production of stem cells while maintaining stemness and differentiation potential. When transplanted into periodontal defects, microcarrier-seeded MSCs enhance cell retention, improve spatial distribution within the defect, and promote regeneration of alveolar bone, periodontal ligament fibers, and cementum [29].

Nanoparticle systems—including polymeric nanoparticles, liposomes, metallic nanoparticles, and bioactive glass nanoparticles—offer precise control over drug, gene, and growth-factor delivery to enhance stem cell-mediated periodontal repair. It delivers osteogenic cues (BMP-2, PDGF, IGF-1), anti-inflammatory agents, or nucleic acids that modulate stem cell differentiation pathways. Their nanoscale size allows deep penetration into periodontal tissues and controlled, sustained release that creates a favorable microenvironment for stem cell survival and regeneration. These, nanoparticles can be incorporated into hydrogels, membranes, or scaffolds to improve mechanical strength, bioactivity, and mineralization capacity.

Collectively, microcarriers and nanoparticle-based technologies improves cell viability, targeting regenerative signals, and creating a bioactive microenvironment conducive to periodontal tissue regeneration. Their integration with MSCs such as DPSCs, PDLSCs, SHED, and GMSCs holds significant translational potential for predictable, biologically driven periodontal reconstruction [30].

5. 3D Bioprinting

Biologically, 3D bioprinting supports the incorporation of various stem cell types such as PDLSCs, DPSCs, GMSCs, and SCAP into hydrogel-based bioinks, enabling high cell viability, guided differentiation, and interface formation. Bioinks composed of gelatin methacrylate, alginate, collagen, fibrin, and decellularized extracellular matrix (dECM) provide a biomimetic microenvironment that enhances osteogenic, fibroblastic, and cementoblastic differentiation. Layer-by-layer fabrication allows the creation of graded constructs.

In periodontal regeneration, 3D-printed scaffolds have shown significant promise in repairing intrabony defects, furcation defects, and large periodontal lesions by enhancing cell retention, guiding tissue organization, and improving mechanical stability. Bioprinted PDL-bone and PDL-cementum interfaces demonstrate improved fiber alignment and attachment reminiscent of native Sharpey's fibers [31].

6. Electrospinning Technology

Electrospinning an advanced scaffold-fabrication technique that produces nanoscale fibers with controlled diameter, porosity, and orientation. These features create surface properties that enhance acellular signaling, gene expression, and stem cell responses—making them well suited for guiding periodontal fiber alignment and supporting alveolar bone formation. Aligned electrospun scaffolds have been shown to direct PDLSC orientation and improve cell adhesion and viability. Studies using multilayered constructs, such as PCE nanofibers embedded in porous chitosan, demonstrated organized PDL regeneration, increased mature collagen fiber formation, and elevated periostin expression in vivo.

Biphasic electrospun scaffolds incorporating calcium-phosphate coated bone compartments further improved osteoconductivity, vascularization, and periodontal attachment.

Certain limitations, includes slow production, high cost, and difficulty generating complex 3D architectures issues that 3D printing technologies are increasingly able to overcome [32].

Analysis methodologies of Stem Cell therapy in Periodontal Regeneration

- **Histological and radiographic analysis:** Radiographic and histological evaluations used to measure the efficacy of stem cell therapy in periodontal regeneration. Histological analysis is performed on tissue samples taken from the treated areas, frequently by biopsy or extraction, the samples are examined under a microscope. Concurrently, non-invasive viewing of the treated area is provided via radiographic pictures, such as X-rays or cone-beam computed tomography (CBCT) scans. Researchers can measure the degree of tissue regeneration and evaluate the overall efficacy of stem cell therapy by comparing these images with untreated controls.

- **Functional assessments:** Restoring tooth stability and function is a crucial part of periodontal regeneration.

Researchers use functional testing, including biting force analysis, to evaluate this. The strength of the bite and the treated teeth's capacity to support functional stresses are measured by these tests. Assessing biting force sheds light on the real-world applications of stem cell-induced periodontal regeneration. It assists in determining whether the treatment improves the patient's capacity to bite and chew while also restoring the structure of periodontal tissues [33].

- **Micro-computed tomography (micro-CT) imaging:** An effective method for evaluating alterations in bone volume and architecture is micro-CT imaging. Bone regeneration may be precisely quantified by the rich three-dimensional images of the treated area. A thorough understanding of the structural alterations inside the treated periodontal tissues is provided by the measurement of metrics such bone volume, trabecular thickness, and bone density. When evaluating the effectiveness of stem cell therapy in rebuilding bone architecture and volume, micro-CT imaging is especially useful [34].

Limitations & regulatory considerations

- **Safety:** Short-term safety in trials is acceptable; infection, immune reactions, or tumorigenicity have been rare in published clinical series, but long-term surveillance is limited. GMP manufacturing, sterility testing, and traceability are mandatory.

- **Ethics:** Autologous cells reduce immune risk but increase cost/time. Allogeneic "off-the-shelf" products (e.g., DPSCs, PDLSC preparations, or exosomes) promise scalability but require robust immunogenicity and safety data. Informed consent must address investigational status and unknown long-term risks.

- **Regulation:** Regulatory classification (biologic, ATMP, tissue-engineered product) varies by jurisdiction. Clinical translation must comply with national regulatory agencies (e.g., CDSCO, FDA, EMA) and local ethics boards.

Cost-effectiveness analyses and patient-reported outcomes are scarce.

Conclusion

Stem cell therapy in periodontics is a promising translational field with growing clinical evidence showing modest but statistically significant improvements in periodontal outcomes versus cell-free controls. Key barriers to routine clinical adoption include heterogeneity of methods, regulatory/manufacturing complexity, cost, and limited long-term safety/efficacy data. Future well-designed and adequately powered RCTs and standardized reporting will be essential to define the most effective cell sources and delivery strategies and to move therapies from experimental to mainstream practice.

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