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Stem cells in dentistry: A comprehensive review of sources, clinical applications, biomaterials, and future challenges

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Abstract
Introduction: Research into stem cells and regeneration in dentistry allows for the development of biological therapies that replace conventional invasive treatments, reduce long-term costs, and improve patients quality of life through the regeneration of dental and bone tissue.
Objective: To analyze the literature on Stem Cells and Regeneration in Dentistry, particularly on a) Sources of Stem Cells in Dentistry, b) Potential Clinical Applications, c) Biomaterials and Scaffolds, and d) Challenges and Future Projections.
Methodology: A search was conducted in the PubMed, Google Scholar, and Scopus databases using the keywords “Stem Cells in Dentistry,” “Biomaterials,” “Scaffolds,” and “Dental Pulp Regeneration”.
Results: Dental stem cells (from pulp, ligament, and dental follicle) are multipotent and essential for the regeneration of dental, periodontal, and bone tissues. In clinical practice, Dental Pulp Stem cells (DPSCs) help regenerate pulp and bone, while Periodontal Ligament Stem Cells (PDLSCs) and Dental Follicle Stem cells (DFSCs) repair ligaments and alveolar bone. The use of biomaterials such as hydrogels, nanostructures, and controlled release systems improves regeneration. However, ethical, regulatory, and standardization challenges remain, as does the risk of uncontrolled differentiation, which requires control and responsible application.
Conclusion: Dental stem cells represent a promising tool for oral tissue regeneration, offering new therapeutic possibilities in dentistry. However, their clinical application requires greater standardization, biological control, and ethical regulation to ensure safe and effective treatments.

Keywords: Stem cells in dentistry, biomaterials, scaffolds, and dental pulp regeneration

1. Introduction

Stem cells play a central role in tissue regeneration in dentistry, forming the basis of what is known as regenerative dentistry [1]. In clinical practice, stem cell regeneration has focused on the dentin-pulp complex, periodontal regeneration, and alveolar bone regeneration [2]. Initial studies demonstrated that mesenchymal stem cells have the ability to repair and regenerate dental and periodontal tissues [3]. Dental tissue engineering combines cells, scaffolds, and growth factors [4], and therapies with DPSCs and their exosomes promote dental regeneration safely and effectively [5]. Regenerative endodontics seeks to restore the vitality and function of immature teeth by inducing new pulp tissue using stem cells, growth factors, and biocompatible scaffolds, offering a minimally invasive alternative to conventional root canal therapy [6]. A review of the literature on stem cells and regeneration in dentistry is important for consolidating scientific advances, identifying effective methods and limitations, evaluating biomaterials and scaffolds, detecting research gaps, and guiding evidence-based clinical decisions. This paper analyzes the literature on stem cells and regeneration in dentistry, mainly sources of stem cells in dentistry, potential clinical applications, biomaterials and scaffolds, as well as challenges and future projections.

2. Methodology
An electronic search was carried out through PubMed, Google Scholar and Scopus, using the terms: "Stem Cells in Dentistry", "Biomaterials", "Scaffolds", and "Dental Pulp Regeneration", using Boolean operators "AND" and "OR". The quality of the articles was evaluated using guidelines tool. As inclusion criteria, only articles from high impact journals were collected, including systematic reviews, literature reviews or clinical studies that treated in behavior management techniques. Likewise, the search was delimited in terms of publication date, taking only recent articles, published mainly within the last 5 years. The selection of articles was made according to the relevance of the title and/or abstract to the topic to be analyzed. After the selection of relevant studies, their references were searched for possible additional relevant studies that met the inclusion criteria.

3. Results
3.1 Sources of stem cells in dentistry
3.1.1 Dental Pulp Stem Cells (DPSCs)
DPSCs are a promising source for the regeneration of dental tissues and other tissues in the body, as they produce odontoblasts and reparative dentin, can be easily isolated from extracted teeth, and, thanks to their origin in the neural crest, have applications in neurology and musculoskeletal medicine [7]. Furthermore, present in the pulp, periodontium, and other dental tissues, they are multipotent and capable of self-renewal, demonstrating in preclinical and clinical studies their ability to improve the formation of specialized dental structures and the repair of damaged tissues [8]. Their differentiation into multiple cell types and the regeneration of the dentin-pulp complex is regulated by growth factors, scaffolds, and mitochondrial function, consolidating them as a key tool for dental regeneration therapies [9].
DPSCs are key multipotent stem cells in dental regeneration, capable of repairing tissues and forming specialized structures, with great potential for regenerative therapies.

3.1.2 Periodontal ligament
Periodontal ligament stem cells (PDLSCs) are multipotent, capable of self-renewal and differentiation into multiple lineages, with angiogenic, immunoregulatory, and anti-inflammatory properties [10], making them promising tools for periodontal and adjacent tissue regeneration [11]. Their ex vivo expansion, optimized by growth factors and special matrices, allows for the development of safe and effective regenerative therapies that can repair periodontal ligament and alveolar bone destroyed by periodontitis, offering an innovative approach in regenerative medicine despite their limited availability [12].
PDLSCs are key multipotent stem cells for periodontal regeneration, capable of repairing ligament and alveolar bone, offering a safe and promising approach to regenerative therapies.

3.1.3 Apical papilla and dental follicle
Dental pulp and the apical papilla are valuable sources of mesenchymal stem cells, such as DPSCs and Stem Cells form Apical Papilla (SCAPs), which share markers and differentiation capacity, making them ideal for dental pulp tissue engineering [13]. Dental follicle stem cells (DFSCs) are precursors of periodontal tissues, capable of differentiating into multiple cell types and showing therapeutic effects in inflammatory and autoimmune diseases, consolidating them as a promising source for cell therapies in dentistry and regenerative medicine [14]. In addition, DFSCs promote periodontal regeneration in inflammatory microenvironments through the expression of periostin, which regulates periodontal homeostasis and modulates the immune response, making them a key therapeutic target for improving periodontal tissue repair [15].
DPSCs, SCAPs, and DFSCs are key stem cells in regenerative dentistry, capable of differentiating into multiple dental and periodontal tissues, modulating the immune microenvironment, and offering great therapeutic potential for dental and periodontal regeneration.

3.2 Potential clinical applications
3.2.1 Dental pulp regeneration
Bone tissue engineering uses DPSCs and scaffolds to repair damaged bone, notable for their multipotency, low immunogenicity, and ease of isolation; Their osteogenic differentiation is regulated by transcription factors and signaling pathways, and studies support their regenerative potential [16]. In addition, DPSCs accelerate skin and mucosal healing through M2 macrophage polarization, VEGF activation, and TGF-β increase, enhanced by extracellular vesicles and conditioned medium, with applications in the oral mucosa, esophagus, colon, and fallopian tubes [17]. These cells also have immunomodulatory and anti-inflammatory capabilities, regulating excessive inflammatory responses and showing therapeutic potential in autoimmune and inflammatory diseases; although most studies are preclinical, their clinical development as an effective therapy is expected [18].
DPSCs show high potential in bone regeneration, tissue healing, and immune modulation, making them promising candidates for regenerative and clinical therapies in inflammatory and chronic diseases.

3.2.2 Periodontal regeneration
Periodontal disease affects the tissues supporting the teeth and can lead to tooth loss. Periodontal surgeries are invasive, including gingival or alveolar bone resection, and surgical and pharmacological approaches seek stable, almost scar-free healing [19]. Periodontal regeneration is a central goal of clinical research, and the use of biomaterials such as guided regeneration membranes and grafts has improved therapeutic outcomes; advances in biomimetic materials and multifunctional scaffolds allow for the regeneration of alveolar bone, periodontal ligament, and cementum [20]. Complete regeneration requires the reconstruction of hard and soft tissues without forming junctional epithelium or ankylosis; GBR/GTR membranes are useful for partial treatments, while multilayer scaffolds combining biomaterials, stem cells, and growth factors show greater potential for comprehensive regeneration of each section of the periodontium, although they present challenges in preparation and efficacy [21].
Periodontal regeneration seeks to comprehensively restore dental support tissues affected by disease, combining surgical approaches, biomaterials, and multifunctional scaffolds with stem cells and growth factors; although these advances show great potential, they still face challenges in their preparation and clinical efficacy.

3.2.3 Tissue engineering for biohybrid implants
Tooth loss with bone resorption represents a significant clinical challenge, and tissue engineering has explored hybrid tooth-bone implants for its treatment. Implants have been

developed using pig molar cells and bone progenitors on PGA/PLGA scaffolds, cultured in rats and bioreactors, which showed dental and bone implant bonding with the formation of dentin, enamel, bone, and connective tissue similar to the periodontal ligament [22]. Similarly, biohybrid implants coated with HA and dental follicle stem cells transplanted into murine models generated fibrous tissue with periodontal ligament and cementum, restoring physiological functions such as bone remodeling and response to noxious stimuli [23]. 3D biohybrid implants also allow for the recovery of mechanical responses and resistance to infections, overcoming the limitations of traditional implants that lack periodontal ligament [24].

Biohybrid dental implants represent a promising advance in the restoration of lost teeth with bone resorption, as they allow for the regeneration of periodontal ligament, bone, and cementum, restoring physiological functions and overcoming the limitations of traditional implants.

3.3 Biomaterials and scaffolds

3.3.1 Hydrogels as three-dimensional supports

Dental tissue-derived stem cells (DSCs) are valuable in regenerative medicine due to their availability, low immunogenicity, and absence of ethical controversies. Their combination with hydrogels has shown the ability to repair soft and hard tissues, facilitating cell differentiation and tissue regeneration [25]. In periodontitis, thermoresponsive hydrogels loaded with emodin have demonstrated antibacterial and anti-inflammatory effects, sustained release, biocompatibility, and reduced bone loss [26]. Hydrogels act as adjustable three-dimensional scaffolds, whether natural, synthetic, or hybrid, that can be biofunctionalized with cell-binding sequences or bioactive molecules to optimize regeneration [27].

Hydrogels combined with dental stem cells represent a promising strategy in tissue regeneration, facilitating tissue repair, cell differentiation, and controlled release of bioactive compounds, with potential application in diseases such as periodontitis.

3.3.2 Nanostructures and bioactive biomaterials

Nanostructures and bioactive biomaterials in regenerative dentistry allow the differentiation of stem cells to be directed and improve dental regeneration through biomimetic scaffolds and nanoparticles for controlled release and diagnosis [28]. In pulp regeneration, nanoparticles facilitate the administration of low-dose antibiotics without affecting cell viability, while nanofibrous scaffolds and bioactive nanomolecules promote stem cell migration, proliferation, and differentiation, supporting pulp-dentin complex repair [29]. In addition, multifunctional nanoparticles doped with copper and loaded with EGF combine antibacterial, proangiogenic, and osteo/odontogenic effects, stimulating stem cells and promoting effective regeneration of damaged tissues [30].

Bioactive nanostructures and biomaterials are key tools in regenerative dentistry, as they enable more precise and effective regeneration of dental pulp by directing cell differentiation, promoting stem cell proliferation and migration, and combining antibacterial and pro-regenerative effects through advanced controlled release systems.

3.3.3 Controlled release systems for growth factors

Controlled release systems for growth factors (GFs) optimize stem cell proliferation and differentiation through biomaterial carriers that allow for sustained and precise release, improving tissue regeneration in dentistry, although challenges remain in their control and integration with tissues [31]. The combination of A-PRF with MTA or Biodentine modifies GF release without affecting the viability or migration of SCAPs, highlighting the need for further studies in endodontic regeneration [32]. Similarly, core-crown hydrogels with GF microparticles offer biocompatible platforms for sequential drug release, showing potential for dentin regeneration and clinical applications [33].

Controlled-release growth factor systems and biocompatible hydrogels improve endodontic regeneration by promoting stem cell proliferation and differentiation without affecting their viability, showing great potential for clinical applications.

3.4 Challenges and future projections

3.4.1 Limitations in standardized clinical protocols

Although dental stem cells have been used clinically for regenerative therapies, variability in manufacturing practices and lack of standardization hinder their application, as do strict regulatory requirements that slow clinical translation [34]. In periodontal regeneration, selecting biomaterials that offer biocompatibility, bioactivity, and stability remains a challenge, and the absence of standardized protocols leads to variable results [35]. Similarly, regenerative endodontics faces challenges due to a lack of uniformity in procedures, although innovations such as gene therapy and 3D bioprinting offer promising solutions [36].

The lack of standardization and regulatory challenges limit the clinical application of stem cells and biomaterials in dentistry, although emerging innovations offer a promising future for dental regeneration.

3.4.2 Risks of uncontrolled differentiation

The risks of uncontrolled differentiation in stem cell therapies are a critical limitation to their clinical application in dentistry. Although dental stem cells have great regenerative potential, they can differentiate into unwanted cell types, causing calcifications or ectopic ossifications, loss of graft functionality, and unpredictable biological responses [37]. Similarly, mesenchymal stem cells (MSCs) used for periodontal regeneration, despite their immunomodulatory capacity, anti-inflammatory effects, and multipotent regeneration of periodontal ligament, alveolar bone, and cementum, can also differentiate into unwanted cell types or form ectopic structures in inappropriate sites [38]. Furthermore, adverse metabolic conditions, such as hyperglycemia in diabetes mellitus, inhibit the proliferation and osteoblastic differentiation of PDLSCs and activate the NF-κB pathway, increasing the expression of proinflammatory cytokines, highlighting how systemic factors can induce uncontrolled differentiation and affect the efficacy of regenerative therapies [39].

Uncontrolled differentiation of stem cells and adverse systemic conditions pose significant challenges to the safety and efficacy of regenerative therapies in dentistry, underscoring the need for strategies that ensure precise control over cell behavior.

3.4.3 Ethical and regulatory aspects of research

In regenerative dentistry, ethical and regulatory aspects are fundamental to ensuring safety, efficacy, and equity in the use of stem cells. The lack of standardized protocols, the need for clear informed consent, the risk of premature commercialization, and the difficulty of complying with strict production and traceability regulations are significant challenges that require stronger regulation and international collaboration [2]. Although stem cell therapies show great clinical potential, they pose specific risks: hESCs involve ethical dilemmas due to the destruction of embryos; iPSCs may differentiate in undesirable ways or acquire malignant transformations; and MSCs, although promising, could promote tumors or have overestimated efficacy [40]. Therefore, research in regenerative dentistry must balance innovation and ethics, ensuring standardized protocols, rigorous supervision, and responsible application of these therapies in clinical practice [41].

The development of stem cell therapies in regenerative dentistry requires a balance between innovation and ethics, ensuring standardized protocols, rigorous supervision, and regulatory compliance to guarantee safety, efficacy, and responsible application in clinical practice.

4. Conclusion

DPSCs and PDLSCs are multipotent stem cells essential for dental and periodontal regeneration, with high potential for tissue repair, bone formation, and immune modulation. Their efficacy can be enhanced through controlled release systems of growth factors and biocompatible hydrogels, although uncontrolled differentiation and adverse systemic conditions highlight the need for strategies that ensure precise and safe control of cell behavior in regenerative therapies.

5. Conflict of Interest

Not available.

6. Financial Support

Not available.

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