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Regenerative Dentistry and Stem Cell-Based Therapies: Recent Developments and Future Perspectives

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Abstract:

Regenerative dentistry represents a revolutionary approach to restoring the biology and physiology of injured oral tissues using stem cell therapy, tissue engineering, and novel biomaterials. Recent developments have shifted the paradigm of traditional treatment methods for oral diseases by introducing biological regeneration approaches to restore dental pulp, periodontal, alveolar bone, and craniofacial tissues. This review discusses recent progress in dental stem cell biology, tissue engineering approaches, biomaterials for tissue regeneration, and the application of stem cell therapy for biological tooth repair in regenerative endodontics, periodontal regeneration, and craniofacial tissue engineering. Also, the newest trends in stem cell exosomes, gene editing, organoids, artificial intelligence, and personalized regenerative medicine are presented. Despite many successes in this field, there are still issues such as safety, immune system compatibility, standardization, ethics, regulatory approval, and clinical practice that hinder its wide application. In the future, further development will be possible only through collaboration between researchers from different fields, clinical protocols, and clinical trials for creating safe and reliable methods. In general, regenerative dentistry is a promising field of modern biological medicine.

Keywords: Regenerative Dentistry; Stem Cell Therapy; Dental Stem Cells; Tissue Engineering; Biomaterials; Regenerative Endodontics; Periodontal Regeneration; Exosomes; Artificial Intelligence; Personalized

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1. INTRODUCTION

Regenerative dentistry is a relatively new branch of medicine that focuses on a paradigm shift in dental practices from mere restoration to the biological regeneration of damaged oral tissues. Such conventional treatments as filling, root canal treatment, dental implants, and prosthetic rehabilitation bring back the functionality of tissues but cannot restore their biological nature[1]. Stem cell biology, tissue engineering, biomaterials, and regenerative medicine have been successfully used to develop technologies that can regenerate pulp, dentin, periodontal tissues, alveolar bone, and even craniofacial tissues[2]. The discovery of dental stem cells in combination with scaffold technology, growth factors, three-dimensional bioprinting, genome editing, exosome therapy, and artificial intelligence has allowed a huge step forward in personalized regenerative dentistry.

Even with all these advancements, there are still some problems facing the use of stem cells in regenerative medicine including issues of stem cell viability, vascularization, immunocompatibility, standardization of manufacturing, safety, ethical questions, and regulation[3]. There have been some promising results in regenerative endodontics, periodontal regeneration, and craniofacial tissue engineering; but most of these treatments are still under investigation. It is therefore very important to understand the current trends in regenerative dentistry including the advances made, scientific evidence, new technologies, and future directions in research[4].

1.1 Background and Context

Regenerative dentistry is an area that involves the integration of stem cell biology, tissue engineering, biomaterials, molecular medicine, and digital technologies to regenerate damaged dental and craniofacial tissues through biological processes rather than replacing them artificially. During the last twenty years, developments in dental stem cell technology, scaffolding techniques, growth factors and regenerative biomaterials have revolutionized the process of dental tissue repair and regenerative medicine applications in dentistry[5]. Growing interest in minimally invasive treatment strategies has fueled the development of methods for regeneration of dental pulp, periodontal ligaments, alveolar bone and craniofacial structures.

1.2 Objectives of the Review

The main aims of this review are:

- To discuss the biology and regeneration ability of stem cell populations commonly applied in regenerative dentistry.
- To consider the latest developments in tissue engineering, biomaterial science, and stem cell-based approaches to the regeneration of oral and craniofacial tissues.
- To analyze the clinical application and outcomes of stem cell-based regenerative dentistry in endodontics, periodontology, and craniofacial regeneration.

- To address the new technological trends, translational issues, regulatory aspects, and future perspectives that could help in clinical implementation of regenerative dental therapies.

1.3 Importance of the Topic

The increased incidence of various dental problems such as dental diseases, periodontal disease, injuries, and craniofacial anomalies has created the need for new approaches that would provide restoration of the structure and function of damaged dental tissues[6]. Regenerative dentistry based on the use of stem cells provides an interesting approach for treating such conditions since it allows achieving the restoration of biological functions along with decreasing morbidity associated with the traditional methods of treatment. In addition, the combination of regenerative medicine and modern technologies including biomaterials, artificial intelligence, personalized medicine, and digital dentistry can change the future of dentistry greatly. Therefore, it is important to be aware of the state-of-the-art of regenerative dentistry.

2. STEM CELL–BASED REGENERATIVE STRATEGIES IN DENTISTRY

Stem cell based regenerative dentistry has revolutionized the old-fashioned paradigm of treating diseases by moving away from treating damaged dental tissues to regeneration of the biological structure and function. Scientific advancements in the areas of stem cell biology, tissue engineering, biomaterials, and regenerative medicine have made it possible to develop biologics that can regenerate dental pulp, periodontal tissues, alveolar bone and craniofacial structures[7]. Dental stem cells have a good proliferation rate, multilineage differentiation capacity, immunomodulatory activity, and the capability of communicating with bioactive scaffolds and signaling factors that makes them highly suitable candidates for regenerative therapy.

2.1 Dental Stem Cells and Their Biological Potential

The use of dental stem cells is considered one of the most prospective sources of mesenchymal stem cells from adults due to their relative accessibility, high capacity for regeneration, and fewer ethical issues associated with them compared to embryonic stem cells. Dental stem cells are derived from diverse dentine tissue and are capable of being transformed into odontoblasts, osteoblasts, chondrocytes, adipocytes, neuronal-like cells, and vascular endothelial cells under certain biological conditions[8]. They provide not only for the regeneration process but also have properties such as self-renewal, immunomodulation, and production of trophic factors.

Of all the types of dental stem cells, dental pulp stem cells (DPSCs) have been studied the most. Obtained from the dental pulp of permanent teeth, DPSCs have great potential to regenerate and grow, which makes them well suited for the regeneration of the pulp-dentin complex and regenerative endodontics. Moreover, DPSCs have neurogenic and angiogenic functions, which help in the vascularization and repair of nerves in the generated tissues.

Periodontal ligament stem cells (PDLSCs) are found in the periodontal ligament and are responsible for the maintenance of periodontal balance. The ability of PDLSCs to regenerate cementum, periodontal ligaments, and alveolar bone tissues is attracting much interest in their use for the regeneration of periodontal defects[9]. Besides their regenerative functions, PDLSCs have immunoregulatory and anti-inflammatory properties that help in repairing inflamed periodontal tissues.

Apical Papilla Stem Cells (SCAPs) are derived from the root apex of the immature permanent tooth and have outstanding proliferative and mineralization properties. They show fast proliferation and excellent odontogenic differentiation capacity, thus serving as one of the most preferable sources of stem cells for regenerative endodontics and root development after pulp necrosis.

Additionally, Dental Follicle Stem Cells (DFSCs) and Gingival Mesenchymal Stem Cells (GMSCs) can be considered as a possible source of stem cells. DFSCs play an important role in the periodontal tissue development, alveolar bone regeneration and craniofacial tissue engineering, while GMSCs can be easily obtained using minimally invasive methods and demonstrate strong immunomodulatory and wound healing properties[10]. Due to the ability of rapid gingival tissues regeneration without significant donor site morbidity, GMSCs are being used in periodontal reconstruction and inflammatory disease treatment.

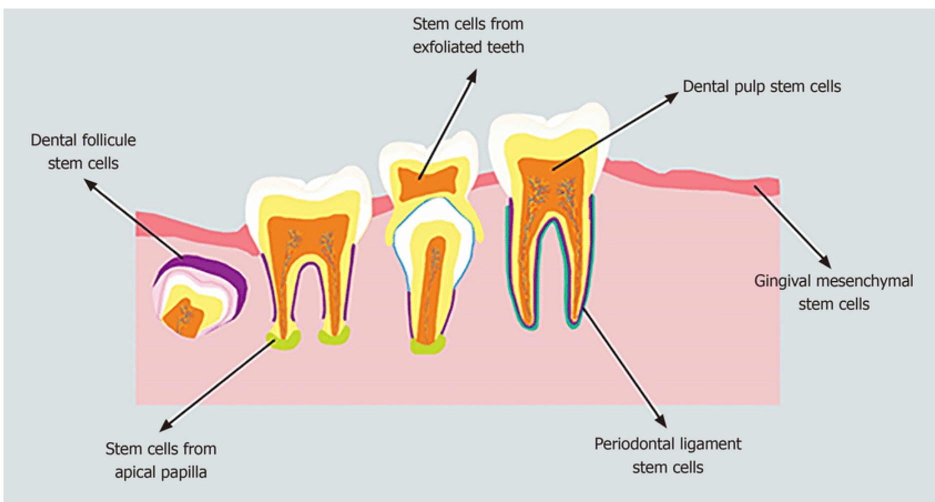

Figure 1. Major Sources of Dental Stem Cells and Their Anatomical Distribution

In conclusion, the existence of several dental stem cells makes it possible for dentists and scientists to choose the right cells depending on their particular purposes. The current studies are mainly concerned with increasing cell viability, directing cells toward certain lineages, bettering vascularization, and promoting host integration[11].

Table 1. Major Dental Stem Cell Types and Their Clinical Applications

Stem Cell Type	Tissue Source	Major Biological Properties	Principal Clinical Applications
Dental Pulp Stem Cells (DPSCs)	Dental pulp	High proliferation, odontogenic, angiogenic, neurogenic	Pulp regeneration, regenerative endodontics, dentin repair
Periodontal Ligament Stem Cells (PDLSCs)	Periodontal ligament	Cementogenic, osteogenic, immunomodulatory	Periodontal regeneration, alveolar bone repair
Stem Cells from Apical Papilla (SCAPs)	Root apical papilla	Rapid proliferation, mineralization, root development	Regenerative endodontics, root maturation
Dental Follicle Stem Cells (DFSCs)	Dental follicle	Osteogenic, periodontal differentiation	Periodontal tissue engineering, craniofacial regeneration
Gingival Mesenchymal Stem Cells (GMSCs)	Gingival connective tissue	Immunomodulation, wound healing, multipotency	Soft tissue regeneration, periodontal therapy, inflammatory disease management

2.2 Tissue Engineering and Biomaterial-Based Regeneration

In addition to stem cells, regeneration of the dental tissues involves an optimal regenerative microenvironment. Tissue engineering is a technology, which combines the use of stem cells, biomaterials, bioactive substances, and biological cues to restore the necessary environment for repair and regeneration of the tissues[12]. Thus, this methodology has become the core of regenerative dentistry.

Biomaterials represent three-dimensional templates, which provide the support for adhesion, proliferation, migration, and differentiation of stem cells. Biocompatible and bioactive natural templates such as collagen, fibrin, gelatin, and chitosan are well-known for their beneficial effects, while mechanically stable and degraded synthetic polymers such as polycaprolactone (PCL), polylactic acid (PLA), and poly (lactic-co-glycolic acid) (PLGA) can be successfully used for fabrication of hybrid templates.

The regenerative capacity of the stem cells can be further increased by growth factors such as bone morphogenetic proteins (BMPs), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor

(PDGF)[13]. Such biochemical signals play a role in cell migration, proliferation, angiogenesis, extracellular matrix generation, and cell differentiation, and cause rapid maturation of the tissue. The use of controlled release technologies in combination with biomaterials has greatly increased the local efficacy of such molecules.

There have been major breakthroughs in the field of hydrogels, bioactive materials, and 3D bioprinting in recent years. Hydrogels can be injected to replicate the extracellular matrix, thereby making the delivery of stem cells a less-invasive process. In addition, bioactive ceramics, calcium phosphate materials, bioactive glass, and nanocomposites are active in mineralizing and stimulating osteogenic differentiation. On the other hand, 3D bioprinting is capable of fabricating patient-specific scaffolds with controlled porosity and with the exact placement of stem cells and bioactive molecules[14]. This technology is moving us towards developing regenerative medicine that would help reconstruct the complex craniofacial and dental tissues.

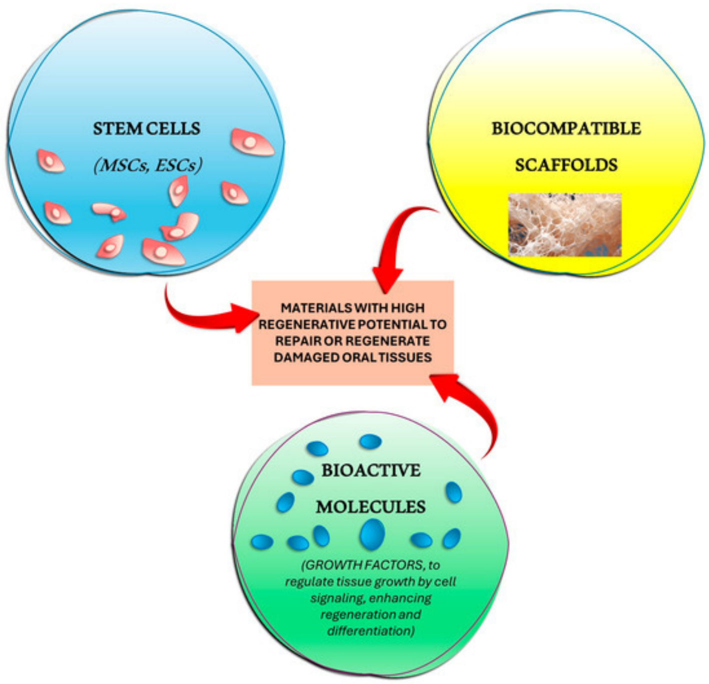

Figure 2. Schematic Illustration of Hybrid Scaffold-Based Dental Stem Cell Tissue Engineering for Regenerative Dentistry

2.3 Clinical Applications in Regenerative Dentistry

The translation of stem cell therapy into the clinic has progressed immensely over the last decade, with regenerative treatment methods being used in various dental specialties. While many methods are still under clinical trials, their success rates have shown promise in their ability to regenerate biological function as opposed to just tissue replacement.

One of the most promising methods is that of regenerative endodontics, where stem cells, growth factors, and scaffold are used to regenerate the pulp-dentin complex of immature teeth whose pulp is dead[15]. This method aids in the continued development of the roots of teeth, thickening of dentinal walls, closing of apices, and vascularization.

Moreover, periodontal regeneration has greatly benefitted from stem cell-based therapy. Several preclinical and clinical trials have reported the ability of PDLSCs, GMSCs, and DFSCs to regenerate periodontal ligament fibers, cementum, and alveolar bone, as well as reduce inflammation and improve wound healing. In combination with guided tissue regeneration membranes, bioactive scaffolds, and growth factors, stem cells have provided improved periodontal attachment and treatment outcome in patients with severe periodontitis.

Bone, craniofacial, and pulp-dentin complex regeneration is another rapidly advancing research field. Tissue engineering using stem cells has been very successful in terms of reconstruction of alveolar bone defects caused by trauma, congenital malformations, periodontitis, and tooth loss. At the same time, recent advancements in scaffold design and engineering, vascularization techniques, and biomaterial development have made possible regeneration of living pulp and dentin[16]. The future of exosomes and extracellular vesicles, gene-modified stem cells, and bioprinting technology promises even greater success of regenerative dentistry.

3. CLINICAL APPLICATIONS OF STEM CELL–BASED REGENERATIVE DENTISTRY

Clinical translation of stem cell therapy into dentistry has been rapidly advancing during the last decade, offering novel biological modalities for regeneration of damaged dental and craniofacial tissues. In contrast to traditional restorative approaches where the lost tissues are usually replaced by artificial means, stem cell regeneration aims at restoring the natural architecture and physiology of the oral tissues[17]. Combination of dental stem cells with bioactive scaffolds, growth factors, and tissue engineering technologies has shown promising results in regenerative endodontics, periodontal regeneration, alveolar bone regeneration, and craniofacial tissue regeneration. Even though many of these therapeutic methods are still in the translational phase, growing preclinical and clinical data suggest that they may be highly beneficial in improving treatment results and maintaining the natural physiological functions of teeth.

3.1 Regenerative Endodontics and Pulp–Dentin Regeneration

Regenerative Endodontics has become one of the best examples of successful implementation of stem cell based regenerative dentistry. The existing root canal therapy is effective in treating infections but does away with the dental pulp causing the loss of tooth vitality and regenerative potential. Regenerative Endodontic Procedures (REPs) have been developed with the objective to overcome these drawbacks and regenerate pulp tissue, dentin formation, and neural innervation inside the root canal space. This is achieved using dental stem cells, growth factors, scaffolds, and correct disinfection techniques[18].

The most remarkable regenerative properties among all the populations of stem cells have been found in dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAPs), owing to their high proliferative properties, odontogenic differentiation, angiogenesis, and root development. Various clinical studies have found success in cases of complete apex formation, increase in the length of the roots, dentinal walls becoming thicker, revitalization of the pulp, and periapical healing after regenerative endodontic treatment of immature permanent teeth with necrotic pulp. In addition to this, the use of platelet-rich plasma, platelet-rich fibrin, collagen scaffold, and biological growth factors has significantly improved the recruitment of stem cells and dentin-pulp regeneration[19].

Some of the recent studies have involved the application of advanced regenerative methods such as cell sheet technology, injectable hydrogels, stem cell derived exosomes, and 3D printing of scaffolds in order to enhance predictability of treatment outcomes and improve its long-term success. Such methods are expected to ensure full regeneration of the pulp-dentin complex without any adverse effects.

3.2 Periodontal and Craniofacial Tissue Regeneration

Periodontal disorders, traumatic dental injuries, congenital craniofacial developmental anomalies, and alveolar bone deficiency continue to pose formidable problems in the field of restorative dentistry due to the complex structure of periodontal and craniofacial tissues. The use of stem cell technology to regenerate these tissues by simultaneously regenerating the alveolar bone, periodontal ligament, cementum, and the surrounding soft tissues has proven to be very promising[20].

The periodontal ligament stem cells have received much attention due to their potential to regenerate the entire periodontal attachment complex along with their immunomodulatory and anti-inflammatory characteristics. In combination with guided tissue regeneration barriers, collagen matrices, bioactive ceramics, and growth factors, periodontal ligament stem cells have proved to be beneficial in terms of enhanced periodontal attachment, decreased inflammation-induced tissue destruction, increased cementogenesis, and alveolar bone formation.

In a similar vein, dental follicle stem cells (DFSCs), gingival mesenchymal stem cells (GMSCs), and mesenchymal stem cells isolated from bone marrow have demonstrated their potential in craniofacial tissue engineering. Highly advanced biomaterials such as hydroxyapatite, β-tricalcium phosphate, bioactive glasses, nanocomposites, and injectable hydrogels give mechanical stability and at the same time promote the processes of osteogenesis, angiogenesis, and deposition of extracellular matrix[21]. Three-dimensional printing and design of patient-specific scaffolds have enabled the precise anatomical adaptation and spatial distribution of regenerative cells and biomolecules, and hence, have significantly contributed to the treatment of complex craniofacial defects.

3.3 Clinical Evidence and Current Therapeutic Outcomes

The increasing amount of scientific research shows that stem cells can be used effectively in regenerative treatment due to its high potential in treatment. Pre-clinical studies and clinical trials proved successful biological effects such as tissue regeneration, wound healing, improved vascularization, inflammation reduction, and restoration of functional dental tissues. Regenerative endodontic treatment showed successful root maturation, dentinal wall thickening, and revival of pulp vitality of immature permanent teeth, and periodontal treatments were successful in terms of clinical attachment level improvement, bone regeneration, and periodontal stabilization.

While these results seem promising, significant variations still exist in published studies owing to the disparity in sources of stem cells, scaffold materials, growth factors used, mode of treatment, patient selection and follow up period[22]. Most of the existing clinical trials have small numbers of patients and follow up periods that prevent standardization of treatment protocol. Additionally, variations in the manufacture process, cell preparation methods and outcome measures make comparisons difficult between the different trials.

However, current scientific studies still prove the safety and biological possibility of stem-cell-based regenerative dentistry techniques, especially in regenerative endodontics and periodontal regeneration. Future multi-center randomized control trials with a standardized approach, sufficient number of patients, and long-term follow-up will be necessary to prove the efficacy of the procedure, improve the strategy, and implement it into the routine dental care.

4. EMERGING TECHNOLOGIES, TRANSLATIONAL CHALLENGES, AND FUTURE DIRECTIONS

Regenerative dentistry has been developing rapidly to move from the application of stem cell transplantation to advanced regenerative platforms that incorporate cell-free therapy, gene editing, artificial intelligence, and precision medicine. Such modern technologies attempt to address many of the challenges faced by classical stem cell therapy, such as low cell survival rates, insufficient vascularization, immune rejection, manufacturing complexity, and lack of consistent results[23]. At the same time, advancements in digital technologies, materials, and personalized treatment planning make it possible to bring regenerative treatments from scientific research into regular clinical practice. Despite the significant progress in regenerative dentistry, there are many biological, technological, regulatory, and ethical issues to be solved before the widespread use of these therapies in clinical settings.

4.1 Emerging Technologies in Regenerative Dentistry

In recent years, advances in technology have greatly improved the application of regenerative dentistry therapy by facilitating tissue regeneration, predicting treatment outcomes, and overcoming some of the drawbacks associated with stem cell transplantation. One of the latest and most promising cell-free therapies is the use of stem cell exosomes. Exosomes are nano-scale extracellular vesicles that transport proteins, lipids, messenger RNA, microRNA, and growth factors which have the ability to modulate cell signaling, angiogenesis, inflammation, and tissue repair. In contrast to live stem cells, exosomes offer low immunogenicity, low tumor formation risk, ease of storage and manipulation, while providing a significant number of regenerative actions of parent cells. For this reason, exosome therapy is widely explored for periodontal, pulp tissue, alveolar bone and soft tissue regeneration[24].

Gene editing through CRISPR-Cas systems is another swiftly growing field allowing for specific editing of genes related to stem cell proliferation, differentiation, mineralization, and regeneration. This technique opens new avenues for boosting the regenerative potential of dental stem cells, correcting congenital anomalies of the skull and face, enhancing the resistance of the cells to inflammation, and stimulating tissue-specific formation. In addition to genetic modification techniques, another popular approach is the organoid technology that has emerged as an advanced in vitro system able to simulate the three-dimensional structure and biological properties of native dental tissues[25].

Further advancement of the use of artificial intelligence (AI) and personalized regenerative medicine in dentistry is also making more changes to regenerative dentistry. Artificial intelligence helps in interpreting images, diagnosing conditions automatically, designing biomaterials, planning treatments, creating scaffolds, and predicting regenerative results through the use of machine and deep learning algorithms[26]. On the other hand, personalized regenerative medicine involves patient-specific stem cells, genomics, imaging, and customized biomaterials in order to develop personalized treatments for the patients.

Table 2. Emerging Technologies in Regenerative Dentistry: Applications, Advantages, and Current Challenges

Technology	Primary Application	Major Advantages	Current Challenges
Stem Cell-Derived Exosomes	Cell-free tissue regeneration, periodontal repair, pulp regeneration	Low immunogenicity, enhanced angiogenesis, anti-inflammatory effects, easier storage than living cells	Standardization of isolation methods, dosage optimization, large-scale production
CRISPR-Based Gene Editing	Enhancement of stem cell function, correction of genetic defects, improved tissue regeneration	Precise genome modification, targeted differentiation, personalized therapy	Off-target mutations, ethical concerns, regulatory approval, long-term safety

Dental Organoids	Disease modeling, regenerative biology research, drug screening	Mimic native dental tissues, improve preclinical evaluation, personalized testing	Limited vascularization, high production cost, early clinical translation
Artificial Intelligence (AI)	Diagnostic imaging, treatment planning, scaffold optimization, outcome prediction	Improved diagnostic accuracy, personalized treatment planning, workflow automation	Data quality, algorithm bias, clinical validation, integration into practice
Personalized Regenerative Medicine	Patient-specific regenerative therapies using autologous stem cells and genomic data	Higher therapeutic precision, reduced immune rejection, individualized treatment	High treatment cost, complex clinical workflow, limited availability of standardized protocols

4.2 Clinical Translation, Challenges, and Regulatory Considerations

Despite the positive results from laboratory experiments and clinical trials, there are numerous difficulties in translating the application of stem cells into practical clinical procedures. One of the major problems is associated with the long-term safety of stem cells, including their uncontrollable growth, the risk of tumorigenesis, genetic instability, ectopic tissue formation, and unpredictable behavior after transplantation[27]. In this regard, standardized methods for the isolation, expansion, and characterization of stem cells are critical for obtaining clinically-safe therapeutic products.

Immune compatibility and interactions between transplanted cells and host tissues are another issue to consider. Although stem cells from one's own body usually provide an advantage over immune rejection, there could be difficulties with the availability and quality of such cells due to age, systemic disease, or lack of appropriate tissue. Stem cells from other donors are more accessible, although there should be considerations related to the immunogenic potential, inflammatory reactions, and graft survival. At the same time, the manufacture of stem cells, biomaterials, and bioengineered structures on a large scale is technologically challenging because it has to meet GMP standards[28].

Apart from scientific and technological considerations, there remain several ethical and regulatory considerations that have the potential to shape the clinical application of regenerative dentistry. The ethical considerations involve informed consent, patient equity, commercialization of stem cell treatments, ethical application of gene-editing technologies, and avoidance of unproven commercial stem cell therapies. The regulators insist on complete information concerning safety, effectiveness, quality, and performance of the products before granting approval for their use in routine practice. Therefore, multicenter clinical trials, guidelines for publication of research data, harmonized regulation across the globe, and post-marketing surveillance would be indispensable for the responsible implementation of stem cell-based treatments in dentistry[29].

4.3 Future Perspectives for Clinical Dentistry

The future trend for regenerative dentistry is believed to move from biological therapy experimentation to integrated clinical treatment platforms incorporating regenerative medicine, technology, biomaterials, and precision healthcare. Among the predicted innovations is the development of chair-side regenerative treatments, whereby stem cells, bioactive scaffolds, and regenerative biomolecules are prepared and utilized in one clinical session, thus decreasing the duration and increasing the convenience of treatment. Such methods may even supersede traditional restorative treatments in favor of biological tissue regeneration.

Further developments in intelligent biomaterials are also expected to improve the results of regeneration. Future scaffolds that are sensitive to alterations in pH levels, temperature, mechanical stress, enzymes, or inflammation, would be able to release growth factors, medications, and other active agents depending on the particular requirements of regenerating tissues[30]. At the same time, the combination of precision dentistry with genomics analysis, banked stem cells, digital imaging, and customized treatment plans would make it possible to develop highly personalized approaches to regenerative medicine.

In addition to this, the combination of regenerative dentistry and digital dentistry that involves the use of Cone-beam Computed Tomography (CBCT), intra-oral scanning, CAD/CAM (computer-aided design/computer-aided manufacturing), 3D printing, artificial intelligence, and robot-assisted techniques is bound to change clinical workflow and increase treatment accuracy. In the future, research in this field needs to focus on randomized clinical trials on a larger scale, development of standard protocols for treatment, safety concerns, cost-effectiveness, and regulatory harmonization across nations in order to build up scientific evidence for clinical applications. By working together through various collaborations, regenerative dentistry seems to be one of the most revolutionary fields of dental care in the coming years[31].

Table 2. Comparative Analysis of Selected Studies on Stem Cell-Based Regenerative Dentistry

Author(s) & Year	**Study Focus**	**Major Findings**	**Research Gap / Limitation**
Thalakiriyawa & Dissanayaka (2024)[32]	Recent advances in regenerative dentistry	Reviewed recent progress in stem cell therapy, tissue engineering, biomaterials, and regenerative clinical applications, emphasizing the	Highlighted the need for standardized clinical protocols, long-term clinical trials, and stronger evidence

		transition toward biologically based dental treatments.	supporting routine clinical implementation.
Umapathy et al. (2025)[33]	Stem cells, biomaterials, and bioactive materials for dental tissue repair	Demonstrated that combining stem cells with advanced biomaterials and bioactive molecules significantly improves regeneration of dental pulp, periodontal tissues, and alveolar bone.	Clinical translation remains limited by manufacturing complexity, regulatory challenges, and insufficient long-term human studies.
Walsh & Hosseinpour (2021)[34]	Paradigm and future perspectives of regenerative dentistry	Discussed the evolution of regenerative dentistry from conventional restorative treatment to biologically driven tissue regeneration and highlighted its future clinical potential.	Emphasized that current regenerative therapies require further validation through well-designed clinical trials before becoming standard clinical practice.
Wang et al. (2023)[35]	Dental stem cell-derived extracellular vesicles (EVs) in regenerative medicine	Reported that extracellular vesicles and exosomes possess strong regenerative, angiogenic, and immunomodulatory properties while avoiding several limitations associated with direct stem cell transplantation.	Standardization of extracellular vesicle isolation, characterization, dosage, and delivery systems remains a major challenge for clinical application.
Widbiller & Galler (2023)[36]	Molecular advances in dental pulp regeneration	Highlighted recent molecular strategies involving stem cells, signaling pathways, scaffold engineering, and growth factors for functional pulp-dentin regeneration.	Further research is required to improve vascularization, neural regeneration, long-term functional outcomes, and successful translation into routine endodontic practice.

5. DISCUSSION

This review proves that regenerative dentistry has transformed from being an experimental scientific area into the most promising field of contemporary dental science thanks to the implementation of stem cell science, tissue engineering, biomaterials, and digital techniques[37]. The literature clearly shows that dental stem cells demonstrate impressive ability to regenerate pulp, dentine, periodontium, alveolar bone, and craniofacial elements while keeping natural tooth function intact. Moreover, due to innovations in such areas as biomaterial science, scaffolds development, exosomes therapy, gene editing, artificial intelligence, and personalized regenerative medicine, regenerative approaches became more precise and efficient. Despite some successful preclinical and clinical studies, there is a number of scientific, technical, ethical, and legal issues which affect the widespread clinical application of stem cell-based regenerative approaches[38].

5.1 Interpretation and Analysis of Findings

Results from this review suggest that stem cell-based regenerative dentistry is progressively making the treatment of dental complications move from traditional tissue replacement therapies to biological tissue regeneration. Stem cells from the dental tissues, specifically dental pulp stem cells, periodontal ligament stem cells, stem cells from the apical papilla, and gingival mesenchymal stem cells have shown remarkable capability in terms of regeneration by virtue of their properties that include cell differentiation, angiogenesis, immunomodulation, and tissue healing[39]. The incorporation of these stem cells with biomaterials, bioactive growth factors, and tissue engineering techniques has resulted in promising results in the fields of regenerative endodontics, periodontal regeneration, and craniofacial reconstruction. Furthermore, novel strategies including exosome therapy, gene editing, organoids, and artificial intelligence are making treatment more predictable[40].

5.2 Implications and Significance

Regenerative dentistry is progressing at a remarkable pace, which has significant consequences for not only clinical practices but also biomedical science. Stem cell therapy can be used in order to maintain the natural dentition, repair tissues' physiological functions, minimize reliance on traditional prosthetics, and achieve improved results for patients in general. The use of technologies such as artificial intelligence, digital dentistry, personalized medicine, and smart biomaterials increases the accuracy of diagnosis, treatment planning, and personalized approach to treatment. All of these multidisciplinary trends are predicted to revolutionize dental treatment in the future by making it minimally invasive, biological, and patient-centered.

5.3 Research Gaps and Limitations

However, despite advances in the field, there are still some limitations preventing the implementation of regenerative dentistry in daily clinical practice. The majority of research available to date focuses on the laboratory experiments, animal models, or small clinical studies with short-term follow-ups. Inconsistencies in stem cells isolation, scaffold design and production, and criteria for clinical evaluation also decrease the consistency of the findings from existing studies. Besides, such questions as immunocompatibility, scale production, cost-effectiveness, ethical issues, and regulatory approval also prevent further implementation of the technique in everyday practice. This review is based on existing literature; therefore, future advancements in technology and new findings in clinical research will probably affect the conclusions stated here.

5.4 Future Research Directions

For future studies, it is important to improve the clinical effectiveness of stem cell regenerative medicine by conducting interdisciplinary research through collaboration between clinicians, biomaterial scientists, molecular biologists, biomedical engineers, and computational experts. More attention needs to be given to improving the clinical viability, vascularization, scaffold design, delivery of growth factors in a controlled manner, and modulating the immune system in addition to cell-free regenerative techniques, including the use of exosomes. Emerging technologies, such as gene editing, artificial intelligence, organoids, three-dimensional printing, and personalized regenerative medicine, need to be explored via multicenter, large-scale, randomized clinical trials with proper protocol and long-term follow-up. Such developments will allow for the advancement of regenerative dentistry from experimental research to evidence-based clinical application.

6. CONCLUSION

The field of regenerative dentistry and the use of stem cells have revolutionized modern dental science with the advent of biological treatments that could restore the integrity, function, and viability of the injured oral tissues. The advancements made in the field of dental stem cell research, tissue engineering, biomaterials, regenerative endodontics, periodontal regeneration, and craniofacial tissue engineering have shown great potential in replacing traditional restoration with biological methods. The upcoming technologies include exosomes, gene editing, artificial intelligence, personalized regenerative medicine, and digital dentistry. However, there is a need to address certain issues regarding safety, standardization of manufacturing, ethical issues, approval of the therapy, and validation of the treatment before its implementation in the clinic. Further research, development, and evidence-based data are needed to make regenerative dentistry an integral part of future oral healthcare.

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