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Review

Regenerative Therapies in the Treatment of Periodontal Defects

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Abstract

Regenerative therapies in periodontics have shown great potential in restoring damaged periodontal tissues. Techniques such as guided tissue regeneration (GTR) and guided bone regeneration (GBR) have been effective in promoting the regeneration of periodontal ligament, cementum, and alveolar bone. These approaches create a conducive environment for cell repopulation and exclusion of non-osteogenic cells, leading to successful periodontal tissue regeneration. Tissue engineering approaches, utilizing stem cells, growth factors, and biomaterial scaffolds, have also shown promise in regenerating multiple periodontal tissues simultaneously. However, challenges such as membrane exposure and infection need to be addressed. Emerging regenerative techniques, including enamel matrix derivatives (EMDs), stem cell-based therapies, growth factor delivery systems, and gene therapies, offer innovative strategies for periodontal defect treatment. Optimization of delivery systems, refinement of biomaterials, and advancements in gene therapy and tissue-specific biomaterials may further enhance the regenerative capacity of periodontal tissues. Despite challenges, regenerative therapies have the potential to revolutionize periodontics and improve clinical outcomes by addressing the root cause of periodontal diseases and promoting long-lasting tissue regeneration.

Keywords: *regenerative therapies, periodontal defects, guided tissue regeneration, guided bone regeneration, tissue engineering*

Introduction

Regenerative therapies in periodontics have revolutionized the treatment of periodontal diseases by offering the potential for restoring lost periodontal tissues, including periodontal ligament, cementum, and alveolar bone. These therapies employ various techniques, biomaterials, and growth factors to stimulate the body's innate regenerative capacity and promote tissue repair. By targeting the root cause of periodontal diseases rather than merely managing the symptoms, regenerative approaches hold great promise for achieving predictable and sustainable clinical outcomes (1).

Regenerative therapies exploit the principles of tissue engineering and wound healing to facilitate the regeneration of periodontal tissues (2). Key elements involved in the regenerative process include cell populations, signaling molecules, and biomaterial scaffolds. Mesenchymal stem cells (MSCs), obtained from various sources such as bone marrow and adipose tissue, play a crucial role in regenerative approaches by differentiating into the desired cell types and releasing trophic factors that promote tissue repair. Growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and bone morphogenetic proteins (BMPs), regulate cell behavior and stimulate tissue regeneration (3). Biomaterial scaffolds provide structural support, enhance cell adhesion and proliferation, and facilitate the guided regeneration of periodontal tissues.

Regenerative therapies have been applied in various clinical scenarios in periodontics, including intrabony defects, furcation involvement, and gingival recession (4). Guided tissue regeneration (GTR) and guided bone regeneration (GBR) techniques have gained considerable popularity in regenerating periodontal defects. GTR employs barrier membranes to selectively inhibit the invasion of epithelial and connective tissue cells, allowing periodontal ligament cells and progenitor cells to populate the defect site (5). GBR employs barrier membranes and bone grafts to create a secluded environment that promotes bone regeneration (6). Additionally, tissue engineering approaches utilizing cell-based therapies, growth factor delivery systems, and three-dimensional scaffolds have shown promise in promoting periodontal tissue regeneration.

Methodology

This study is based on a comprehensive literature search conducted on June 14, 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed regenerative therapies in the treatment of periodontal defects. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Periodontal diseases are inflammatory conditions characterized by the destruction of periodontal tissues, including the periodontal ligament, cementum, and alveolar bone. Conventional treatment approaches focus on managing disease progression and alleviating symptoms but often fall short in achieving true periodontal tissue regeneration. Regenerative therapies, on the other hand, aim to restore the damaged periodontal tissues, promote tissue regeneration, and ultimately restore optimal periodontal health (1). This comprehensive review presents a classification and description of various periodontal regenerative therapies, providing insights into their mechanisms of action, clinical applications, and limitations.

Among the regenerative techniques, GTR has emerged as a valuable treatment modality. GTR utilizes barrier membranes to create a protected environment that supports the regeneration of periodontal tissues. GTR harnesses the principles of selective cell repopulation and tissue exclusion (7). Barrier membranes act as physical barriers,

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preventing the migration of epithelial and connective tissue cells into the defect site while allowing for the colonization of periodontal ligament cells and progenitor cells. This selective repopulation promotes periodontal tissue regeneration by facilitating the formation of new cementum, periodontal ligament, and alveolar bone. GTR is a versatile technique employed in various clinical scenarios. In the treatment of intrabony defects, GTR is used to promote the regeneration of periodontal tissues within the bony defect (8). By creating a secluded environment, GTR facilitates the formation of new bone, periodontal ligament, and cementum, leading to improved clinical outcomes. Furcation involvements, which present a challenge due to their complex anatomy, can also be effectively managed using GTR (9). The use of barrier membranes in furcation areas aids in maintaining the space necessary for the regeneration of periodontal tissues. GTR is also utilized in the treatment of gingival recession, where the placement of membranes helps to protect the exposed root surface and promote the regeneration of periodontal tissues, including the gingival attachment and connective tissue (10). Numerous clinical studies have demonstrated the efficacy of GTR in promoting periodontal tissue regeneration and improving clinical parameters (8, 11, 12). Successful GTR outcomes are characterized by the reduction of probing depths, gain in clinical attachment level, and increased radiographic bone fill. Moreover, GTR has been shown to enhance the long-term stability of treated sites, leading to improved periodontal health and functional outcomes. Meta-analyses and systematic reviews have reported overall success rates ranging from 50% to 90% for intrabony defects, furcation involvements, and gingival recession treatments (11-13). Despite its success, GTR is not without limitations and challenges. Membrane exposure and infection remain significant concerns, as they can compromise the regenerative potential of GTR (14). Achieving and maintaining proper membrane adaptation and stability is crucial for successful outcomes.

GBR is a technique that combines barrier membranes with bone graft materials to facilitate bone regeneration in periodontal defects (15). The barrier membrane serves to prevent the migration of soft tissue cells into the defect site, creating a space for osteogenic cells to populate and promote new bone formation. GBR relies on the principles of space maintenance and exclusion of non-osteogenic cells. Bone graft materials provide structural support and serve as a scaffold for bone regeneration. Additionally, the barrier membrane acts as a barrier to stabilize the bone graft material and prevent its migration, allowing undisturbed bone regeneration to occur.

GBR has versatile clinical applications and is employed in various scenarios. GBR is particularly effective in treating osseous defects associated with periodontal diseases and implant therapy (16). In the treatment of intrabony defects, GBR is used to promote the regeneration of periodontal tissues within the bony defect. The barrier membrane, in conjunction with bone graft materials, facilitates the formation of new bone, periodontal ligament, and cementum, leading to improved clinical outcomes (17). Furcation involvements, which present complex anatomical challenges, can also be effectively managed using GBR (18). The use of barrier membranes and bone grafts aids in maintaining the space necessary for the regeneration of periodontal tissues. Furthermore, GBR plays a crucial role in the treatment of implant-related osseous defects, ensuring adequate bone volume and stability for successful implant placement (19).

GBR has demonstrated favorable clinical outcomes and success rates in the treatment of periodontal defects. Successful GBR outcomes are characterized by the gain in clinical attachment level, reduction in probing depths, and radiographic evidence of bone fill (20). GBR promotes bone regeneration, leading to improved functional and esthetic outcomes.

Although GBR has shown significant success, certain limitations and challenges exist. Membrane exposure and infection are concerns that can

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compromise the regenerative potential of GBR (21). Proper membrane adaptation and stability are critical for successful outcomes (22). Additionally, the selection of appropriate bone graft materials and achieving optimal stability are important factors to consider for successful bone regeneration (23).

Tissue engineering approaches offer innovative strategies for the regeneration of multiple periodontal tissues, including periodontal ligament, cementum, and alveolar bone (24). Tissue engineering involves the integration of cells, biomaterial scaffolds, and bioactive molecules to promote tissue regeneration (1). Mesenchymal stem cells (MSCs) are central to tissue engineering approaches as they possess the capacity to differentiate into periodontal ligament cells, cementoblasts, and osteoblasts (25). MSCs can be derived from various sources, including bone marrow and adipose tissue. Growth factors and signaling molecules, such as PDGF, TGF-β, and BMPs play critical roles in regulating cell behavior, proliferation, and differentiation. Biomaterial scaffolds provide structural support, enhance cell adhesion and proliferation, and facilitate the guided regeneration of periodontal tissues (26).

Tissue engineering approaches have demonstrated promising outcomes in preclinical and clinical studies. In intrabony defects, tissue engineering techniques have shown the potential to regenerate periodontal ligament, cementum, and alveolar bone concurrently (27). The use of MSCs, either alone or in combination with biomaterial scaffolds and growth factors, has resulted in improved clinical parameters, including reduced probing depths and gain in clinical attachment level. Tissue engineering approaches have also shown potential in the treatment of furcation involvements, where the regeneration of periodontal tissues in complex anatomical structures is challenging. Moreover, tissue engineering strategies hold promise for enhancing soft tissue regeneration in gingival recession, leading to improved esthetic outcomes (28).

Although tissue engineering approaches have shown promising results, several challenges need to be addressed for their widespread clinical implementation. Standardization of protocols and techniques is crucial to ensure reproducibility and comparability of results across studies (29). Long-term clinical evidence is necessary to validate the efficacy, safety, and long-term stability of tissue-engineered constructs. Further optimization of biomaterial scaffolds, including their mechanical properties, degradation rates, and bioactivity, is essential for achieving optimal tissue regeneration. Additionally, advancements in gene therapy, advanced manufacturing techniques (e.g., 3D printing), and tissue-specific biomaterials hold promise for further enhancing the regenerative capacity of periodontal tissues.

While established techniques such as GBR, GTR, and tissue engineering approaches have shown promising results, emerging regenerative techniques offer innovative strategies for periodontal defect treatment. Enamel Matrix Derivatives (EMDs) contain enamel matrix proteins, particularly amelogenins, which play a crucial role in tooth development and periodontal tissue regeneration (30). EMDs have demonstrated the ability to stimulate periodontal tissue regeneration, including the formation of new cementum, periodontal ligament, and alveolar bone. These derivatives are often utilized in conjunction with conventional periodontal therapies to enhance clinical outcomes and promote periodontal wound healing (31). Stem cell-based therapies utilize mesenchymal stem cells (MSCs), either derived from the patient's own tissues or from alternative sources, to promote periodontal tissue regeneration (32). MSCs possess the ability to differentiate into various cell types within the periodontium, including periodontal ligament cells, cementoblasts, and osteoblasts. These cells can be isolated and expanded in vitro before being transplanted into the defect site, facilitating tissue regeneration and promoting functional recovery. Growth factors play a crucial role in regulating cell behavior, proliferation, and differentiation during periodontal tissue regeneration (33). Delivery systems for growth

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factors, such as PDGF, TGF-β, and BMPs have been developed to enhance their effectiveness. These systems aim to provide sustained and localized delivery of growth factors to the defect site, promoting the recruitment and proliferation of cells involved in periodontal tissue regeneration. Gene therapies involve the delivery of specific genes to modulate the regenerative capacity of cells and promote tissue regeneration (34). Through the introduction of genes encoding growth factors, transcription factors, or signaling molecules, gene therapies can enhance the regenerative potential of cells involved in periodontal tissue repair. These approaches offer targeted and precise control over the regenerative process, potentially revolutionizing periodontal defect treatment. Although emerging regenerative techniques show promise, further research, standardization, and clinical validation are essential for their successful translation into clinical practice. Clinical trials and long-term studies are needed to evaluate the safety, efficacy, and long-term stability of these techniques. Optimizing delivery systems, improving the understanding of underlying mechanisms, and exploring innovative strategies, such as tissue-specific biomaterials and advanced manufacturing techniques, hold potential for further enhancing the regenerative capacity of periodontal tissues.

The different types of periodontal regenerative therapies have demonstrated clinical efficacy in various applications. GTR and GBR techniques have shown positive outcomes in the treatment of intrabony defects, furcation involvements, and gingival recession. These techniques promote periodontal tissue regeneration and improve clinical outcomes. Tissue engineering approaches have the potential to revolutionize periodontal regenerative therapy by enabling the regeneration of multiple periodontal tissues simultaneously (1). However, the clinical translation and standardization of tissue engineering approaches remain challenging, and long-term studies are needed to establish their efficacy and safety. Emerging regenerative techniques, such as EMDs, stem cell-based therapies, growth factor delivery systems, and gene therapies, hold immense promise but require further research and clinical validation to determine their clinical effectiveness and long-term stability (35).

Despite significant advancements, regenerative therapies in periodontics face several challenges that hinder their widespread clinical implementation. These challenges include the selection of suitable cell sources, optimization of biomaterials and growth factor delivery systems, and the need for long-term clinical evidence of efficacy and safety (1). Future research should focus on refining regenerative protocols, improving the understanding of cell signaling mechanisms, and developing innovative biomaterials with enhanced regenerative potential. Moreover, advancements in gene therapy, tissue engineering, and nanotechnology hold immense potential for further augmenting the regenerative capacity of periodontal tissues.

Conclusion

Regenerative therapies have transformed the field of periodontics, offering new avenues for the restoration and regeneration of periodontal tissues. The integration of cell-based therapies, growth factors, and biomaterial scaffolds has shown promising results in clinical applications. Despite challenges, ongoing research and technological advancements hold great promise for optimizing regenerative protocols, enhancing clinical outcomes, and ultimately improving the quality of life for patients with periodontal diseases. The future of regenerative therapies in periodontics appears bright, heralding a new era of regenerative dentistry.

Disclosure

Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection, and final writing of the manuscript.

References

1. Chen F-M, Jin Y. Periodontal tissue engineering and regeneration: current approaches and expanding opportunities. Tissue Engineering Part B: Reviews. 2010;16(2):219-55.

2. He X-T, Wu R-X, Chen F-M. Periodontal tissue engineering and regeneration. Principles of Tissue Engineering: Elsevier; 2020. p. 1221-49.

3. Mundy GR. Regulation of bone formation by bone morphogenetic proteins and other growth factors. Clinical Orthopaedics and Related Research®. 1996;324:24-7.

4. Cortellini P, Tonetti MS. Clinical concepts for regenerative therapy in intrabony defects. Periodontology 2000. 2015;68(1):282-307.

5. Wang H-L, MacNeil RL. Guided tissue regeneration: Absorbable barriers. Dental Clinics of North America. 1998;42(3):505-22.

6. Elgali I, Omar O, Dahlin C, Thomsen P. Guided bone regeneration: materials and biological mechanisms revisited. European journal of oral sciences. 2017;125(5):315-37.

7. Nyman S. Bone regeneration using the principle of guided tissue regeneration. Journal of Clinical Periodontology. 1991;18(6):494-8.

8. Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. Annals of periodontology. 2003;8(1):266-302.

9. Pontoriero R, Nyman S, Lindhe J, Rosenberg E, Sanavi F. Guided tissue regeneration in the treatment of furcation defects in man. Journal of Clinical Periodontology. 1987;14(10):618-20.

10. Tinti C, Vincenzi G, Cocchetto R. Guided tissue regeneration in mucogingival surgery. Journal of periodontology. 1993;64:1184-91.

11. Needleman I, Tucker R, Giedrys-Leeper E, Worthington H. A systematic review of guided tissue regeneration for periodontal infrabony defects. Journal of periodontal research. 2002;37(5):380-8.

12. Al-Hamdan K, Eber R, Sarment D, Kowalski C, Wang HL. Guided tissue regeneration-based root coverage: Meta-analysis. Journal of Periodontology. 2003;74(10):1520-33.

13. Kao RT, Nares S, Reynolds MA. Periodontal regeneration–intrabony defects: a systematic review from the AAP regeneration workshop. Journal of periodontology. 2015;86:S77-S104.

14. Abdo VL, Suarez L, de Paula LG, Costa RC, Shibli J, Feres M, et al. Underestimated microbial infection of resorbable membranes on guided regeneration. Colloids and Surfaces B: Biointerfaces. 2023:113318.

15. Liu J, Kerns DG. Suppl 1: Mechanisms of guided bone regeneration: A review. The open dentistry journal. 2014;8:56.

16. Jimi E, Hirata S, Osawa K, Terashita M, Kitamura C, Fukushima H. The current and future therapies of bone regeneration to repair bone defects. International journal of dentistry. 2012;2012.

17. Aslan M, Simsek G, Dayl E. Guided bone regeneration (GBR) on healing bone defects: a histological study in rabbits. J Contemp Dent Pract. 2004;2(5):114-23.

18. Martinez Luna AA, Gholami F. Management of Furcation Defects. Advances in Periodontal Surgery: A Clinical Guide to Techniques and Interdisciplinary Approaches. 2020:117-33.

19. Monje A, Pons R, Insua A, Nart J, Wang HL, Schwarz F. Morphology and severity of peri-

 http://dx.doi.org/10.52533/JOHS.2023.30802

implantitis bone defects. Clinical Implant Dentistry and Related Research. 2019;21(4):635-43.

20. Chan HL, Lin GH, Suarez F, MacEachern M, Wang HL. Surgical management of peri-implantitis: A systematic review and meta-analysis of treatment outcomes. Journal of periodontology. 2014;85(8):1027-41.

21. Garcia J, Dodge A, Luepke P, Wang HL, Kapila Y, Lin GH. Effect of membrane exposure on guided bone regeneration: A systematic review and meta-analysis. Clinical oral implants research. 2018;29(3):328-38.

22. Buser DA, Tonetti M. Clinical trials on implants in regenerated bone. Annals of periodontology. 1997;2(1):329-42.

23. Sbricoli L, Guazzo R, Annunziata M, Gobbato L, Bressan E, Nastri L. Selection of collagen membranes for bone regeneration: A literature review. Materials. 2020;13(3):786.

24. Ivanovski S, Vaquette C, Gronthos S, Hutmacher D, Bartold P. Multiphasic scaffolds for periodontal tissue engineering. Journal of dental research. 2014;93(12):1212-21.

25. Han J, Menicanin D, Gronthos S, Bartold P. Stem cells, tissue engineering and periodontal regeneration. Australian dental journal. 2014;59:117-30.

26. Liang Y, Luan X, Liu X. Recent advances in periodontal regeneration: A biomaterial perspective. Bioactive materials. 2020;5(2):297-308.

27. Galli M, Yao Y, Giannobile WV, Wang H-L. Current and future trends in periodontal tissue engineering and bone regeneration. Plastic and aesthetic research. 2021;8.

28. McGue CM, Mañón VA, Viet CT. Advances in Tissue Engineering and Implications for Oral and Maxillofacial Reconstruction. Journal of the California Dental Association. 2021;49(11):685.

29. Kaur G, Kumar V, Baino F, Mauro JC, Pickrell G, Evans I, et al. Mechanical properties of bioactive glasses, ceramics, glass-ceramics and composites: State-of-the-art review and future challenges. Materials science and engineering: C. 2019;104:109895.

30. Bosshardt DD. Biological mediators and periodontal regeneration: a review of enamel matrix proteins at the cellular and molecular levels. Journal of clinical periodontology. 2008;35:87-105.

31. Miron R, Dard M, Weinreb M. Enamel matrix derivative, inflammation and soft tissue wound healing. Journal of periodontal research. 2015;50(5):555-69.

32. Satija NK, Singh VK, Verma YK, Gupta P, Sharma S, Afrin F, et al. Mesenchymal stem cell-based therapy: a new paradigm in regenerative medicine. Journal of cellular and molecular medicine. 2009;13(11-12):4385-402.

33. Subbiah R, Guldberg RE. Materials science and design principles of growth factor delivery systems in tissue engineering and regenerative medicine. Advanced healthcare materials. 2019;8(1):1801000.

34. Rios HF, Lin Z, Oh B, Park CH, Giannobile WV. Cell-and gene-based therapeutic strategies for periodontal regenerative medicine. Journal of periodontology. 2011;82(9):1223-37.

35. Chen F-M, Sun H-H, Lu H, Yu Q. Stem cell-delivery therapeutics for periodontal tissue regeneration. Biomaterials. 2012;33(27):6320-44.

http://dx.doi.org/10.52533/JOHS.2023.30802