

Periodontal Renaissance: Pioneering biomaterials and nano-innovations for regenerative excellence in periodontics

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Abstract

The field of periodontics has witnessed a remarkable transformation known as the "**Periodontal Renaissance**," driven by groundbreaking advancements in biomaterials and nanotechnology. These innovations have revolutionized regenerative therapies for periodontal diseases, with the aim of promoting tissue repair and achieving regenerative excellence. This comprehensive paper presents an in-depth review of pioneering biomaterials and nano-innovations utilized in modern periodontics, elucidating their underlying principles, advantages, and potential clinical applications. The integration of figures enhances the understanding of these novel approaches, showcasing their significant impact on periodontal care and patient outcomes.

Keywords: Periodontics, Biomaterials, Nanotechnology, Regenerative therapies, Tissue engineering, Guided tissue regeneration, Guided bone regeneration.

Introduction

Periodontal diseases, encompassing gingivitis and periodontitis, are prevalent conditions affecting millions of individuals worldwide and pose significant challenges to dental professionals. Periodontitis is a multifactorial inflammatory disease that affects nearly 20%–50% of the global population.¹ Its clinical signs include the inflammation and destruction of the periodontium, the supporting structure of the tooth composed of gingiva, periodontal ligament, cementum, and alveolar bone.² Traditional treatments have primarily focused on managing symptoms, but recent developments in biomaterials and nanotechnology have ushered in a new era of regenerative periodontal therapies. The concept of the "Periodontal Renaissance" embodies this transformation, emphasizing the integration of pioneering techniques to stimulate tissue regeneration and restore periodontal health. Biomaterials, bioactive molecules (e.g., growth factors), and (stem) cells are the three critical factors behind the management of periodontal disease (see Figure 1).³

effective in stabilizing periodontal status and maintaining periodontal health.^{4,5} This therapeutic modality has resulted primarily in repair rather than regeneration of the periodontium. Periodontal regeneration is unique because it involves both soft (gingival and periodontal ligament) and mineralized (bone and cementum) connective tissues. Current therapies for periodontal tissue repair and regeneration include conservative approach, radicular conditioning, bone grafting/substitution, and guided tissue regeneration (GTR), as well as a combination of the two last strategies.³ Complete regeneration may be an unrealistic goal for many situations; due in part to the complexity of the biological events, factors and cells underlying successful periodontal regeneration.

This review/comprehensive paper aims to provide an in-depth exploration of the Periodontal Renaissance, focusing on the remarkable contributions of biomaterials and nanotechnology to the field of periodontics

In this paper, we will delve into the various biomaterials utilized in periodontal regeneration, such as guided tissue regeneration (GTR) and guided bone regeneration (GBR) membranes. Moreover, the integration of nanotechnology in periodontics has opened up new frontiers in tissue engineering. We will explore the use of nanomaterials for enhanced drug delivery, nanoscale scaffolds for tissue regeneration, and bioactive nanoparticles incorporated into dental materials to improve treatment outcomes.

Delving into Periodontal Regeneration: A Comprehensive Examination

Tissue engineering has emerged as a promising approach to address the challenges of periodontal diseases by regenerating the damaged periodontal tissues. Currently, the focus of tissue-engineering strategies in periodontal treatment primarily revolves around the regeneration of the alveolar bone using scaffold-based constructs. These

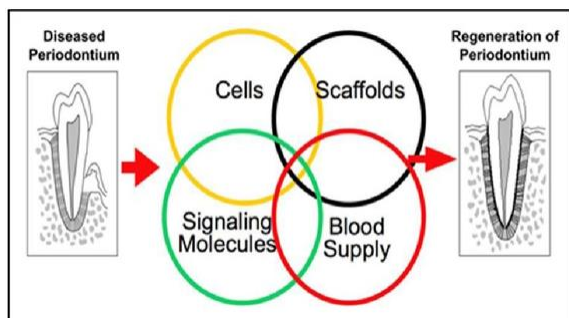


Figure 1: Four basic elements of regeneration

Conventional periodontal therapy consists of scaling, root planing, gingival curettage, gingivectomy and flap procedures of various types, including osseous surgery is

constructs act as three-dimensional (3D) templates, providing structural support for the growth of new tissue. The fundamental principles of periodontal regeneration through tissue engineering can be summarized into four basic paradigms:⁶
Scaffold as a 3D Template⁷⁻⁹: The implantation of suitable Scaffolds provides a structural framework that mimics the natural extracellular matrix (ECM) of the periodontal tissues. These scaffolds are biocompatible and biodegradable, allowing them to be gradually replaced by new tissue as it forms. They serve as an architectural support, guiding the organization and growth of cells to regenerate the damaged periodontal structures.

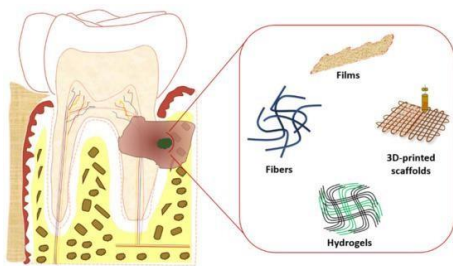


Figure 2. Schematic representation of the main scaffolds used in periodontitis and periodontal regeneration.^{7,8,9}

Cells as Building Blocks: Cells play a pivotal role in the reconstructive strategies for periodontal tissues. Various types of stem cells, such as mesenchymal stem cells (MSCs), dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), and bone marrow-derived stem cells (BMSCs), are utilized in tissue engineering approaches.¹⁰

These cells possess the unique ability to proliferate and differentiate into different cell types, including osteoblasts, cementoblasts, and fibroblasts, essential for the regeneration of the periodontal tissues.

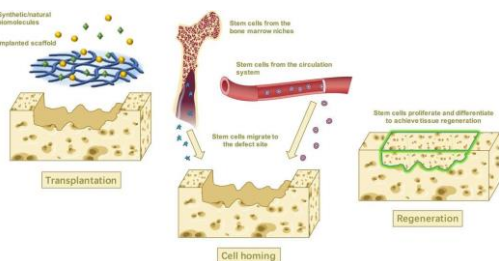


Figure 3: In situ tissue engineering uses biological molecular and scaffolds to recruit the stem cells from the niches while promoting proliferation and differentiation and achieving tissue regeneration in the end.¹⁰

Bioactive Molecules¹¹: Growth factors are bioactive molecules that play a crucial role in promoting cell activity, enhancing cell proliferation, and guiding cell differentiation. These growth factors are incorporated into the scaffold-based constructs or administered separately to stimulate

and accelerate the regeneration process. Some common growth factors used in periodontal regeneration include platelet-derived growth factors (PDGF), transforming growth factor-beta (TGF- β), bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF).

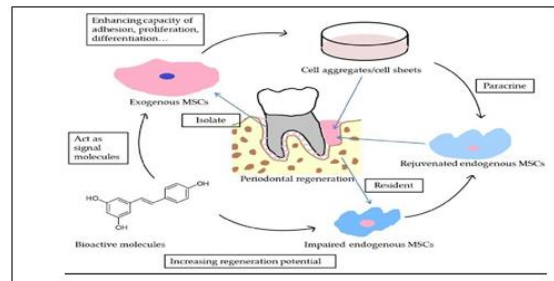


Figure 4: A schematic diagram of the contributions of bioactive molecules in stem cell-based periodontal regeneration. The bioactive molecules could act as signal molecules enhancing the vitality of both endogenous and exogenous MSCs, increasing the regeneration potential of cell aggregates/cell sheets and facilitating periodontal regeneration.¹¹

Blood Supply and Homeostasis¹²: Adequate blood supply is vital for the survival and growth of newly formed tissue within the 3D scaffold. The vascular network delivers oxygen, nutrients, and essential factors to the regenerating tissue, supporting its development and maintenance. An established blood supply also helps to maintain homeostasis and aids in the removal of waste products from the regenerating tissue.

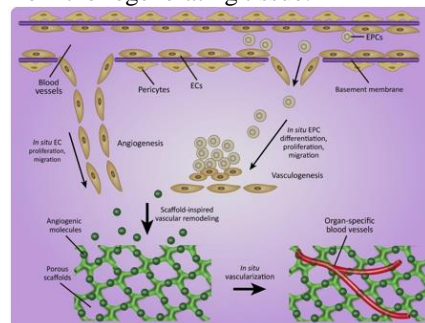


Figure 5: Scaffold-inspired In situ vascularization.¹²

By combining these four fundamental paradigms, tissue-engineering strategies aim to create a conducive microenvironment that supports and promotes the regeneration of functional periodontal tissues. While significant progress has been made in this field, challenges remain, such as achieving optimal cell integration, creating robust and long-lasting scaffolds, and achieving predictable and consistent clinical outcomes. Continued research and advancements in tissue engineering hold the promise of revolutionizing periodontal treatment, offering more effective and patient-specific regenerative solutions to

combat periodontal diseases and improve overall oral health

Contemporary Approaches for Periodontal Regeneration

Guided tissue regeneration (GTR) membranes

The Melcher's hypothesis states that certain cell types under the appropriate conditions can populate the periodontal wound and regenerate new cementum, alveolar bone, and periodontal ligament.¹³

Guided tissue regeneration involves the use of barrier membranes to create a secluded space, promoting the selective repopulation of periodontal cells and suppressing unwanted epithelial and connective tissue ingrowth. Various types of barrier membranes, including resorbable and non-resorbable materials, have been developed to enhance periodontal tissue regeneration.

A. Periodontal guided tissue regeneration (GTR) technique using a barrier me

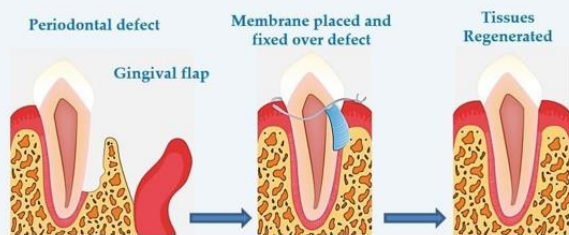


Figure 6: GTR is a surgical procedure that utilizes membranes to regenerate soft tissues. The membrane serves as an occlusive barrier that creates a secluded space around the defect, thus providing an opportunity for the periodontal tissues to regenerate.¹⁴

In the early 1980s, cellulose acetate filter was used as the first material in the role of a barrier membrane and its efficacy for the guided-tissue process was histologically proven.¹⁵

Since then, different types of barrier materials have been developed and clinically experimented.

1. **Resorbable Membranes:** Resorbable membranes are made of materials that degrade over time within the body. They eliminate the need for a second surgery to remove the membrane. These membranes are typically composed of synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA) or polyglycolic acid (PGA), which gradually break down and are resorbed by the body. Resorbable membranes are well-suited for small-to-medium-sized defects.
2. **Non-Resorbable Membranes:** Non-resorbable membranes are made of materials that maintain their structural integrity over an extended period. They require a second surgical intervention to remove the membrane once the desired regeneration has occurred. Common non-resorbable membranes include expanded polytetrafluoroethylene (ePTFE) and high-density polytetrafluoroethylene (dPTFE). Non-resorbable

membranes are preferred for larger defects and situations where prolonged mechanical support is necessary.

3. **Membrane Fixation:** The proper fixation of the barrier membrane is crucial for the success of GTR. Membrane fixation can be achieved using techniques such as sutures, tacks, pins, or collagen plugs. The primary objective is to stabilize the membrane to prevent its collapse during the initial healing period.

Principles of Guided Tissue Regeneration

GTR is based on fundamental principles of wound healing and tissue regeneration. The ultimate goal of GTR is to exclude undesirable cell types, primarily gingival connective tissue, from entering the periodontal defect while facilitating the repopulation of desirable cell populations, including periodontal ligament fibroblasts and osteoblasts.

The guiding principles of GTR include

1. **Cell Exclusion:** The barrier membrane acts as a physical barrier, preventing the migration of undesired gingival tissue cells into the defect site. This exclusion is crucial to create a space for the repopulation of specialized cells responsible for periodontal tissue regeneration.
2. **Space Provision:** The barrier membrane creates a secluded and protected environment, allowing periodontal ligament cells and bone-forming cells to repopulate the defect area unimpeded. This space provision is vital for the re-establishment of periodontal attachment and bone regeneration.
3. **Blood Clot Stabilization:** The barrier membrane stabilizes the blood clot within the defect, promoting the formation of a favorable microenvironment for cell attachment and tissue regeneration.
4. **Stability and Space Maintenance:** The barrier membrane must have sufficient mechanical stability to maintain the created space during the initial healing period. It should resist collapse or dislodgment to support undisturbed regeneration.

Clinical Applications of Guided Tissue Regeneration

GTR has demonstrated clinical success in various periodontal situations, including:

1. **Intrabony Defects:** Intrabony defects occur when there is bone loss around a single tooth root, resulting in a concave defect. GTR is effective in promoting the regeneration of periodontal tissues within these defects, leading to improved clinical attachment levels and bone fill.
2. **Furcation Defects:** Furcation defects occur in multi-rooted teeth, where bone loss extends into the space between the roots. GTR can be used to promote the regeneration of periodontal tissues in furcation-

involved teeth, thereby enhancing tooth survival and preventing further progression of the disease.

3. **Horizontal and Vertical Ridge Augmentation:** GTR has shown promise in horizontal and vertical ridge augmentation procedures, where additional bone volume is required for successful implant placement.
4. **Gingival Recession Coverage:** GTR, in combination with connective tissue grafts or graft substitutes, can be used to cover exposed tooth roots and treat gingival recession defects.

Clinical Success and Limitations

GTR has demonstrated favorable clinical outcomes in promoting periodontal tissue regeneration and improving treatment outcomes. Studies have shown that GTR can lead to significant improvements in probing depths, clinical attachment levels, and bone fill within periodontal defects. However, GTR also has some limitations and challenges:

1. **Patient Compliance:** Successful GTR outcomes are dependent on patient compliance with post-operative instructions, including proper oral hygiene and regular follow-up visits. Poor compliance can compromise the success of the regenerative procedure.
2. **Site Anatomy:** The anatomy and location of the periodontal defect can influence the success of GTR. Certain anatomical factors, such as thin gingival biotype or unfavorable root morphology, may impact the stability and integrity of the barrier membrane.
3. **Membrane Exposure:** Membrane exposure during the healing period can lead to infection and jeopardize the regenerative process. Maintaining proper soft tissue coverage over the membrane is critical for successful regeneration.

Guided Bone Regeneration (GBR)

GBR techniques combine barrier membranes with bone graft materials to stimulate bone formation in areas with bone defects, such as alveolar ridge deficiencies. Different biomaterials, including synthetic bone graft substitutes and autografts, are explored in terms of their ability to support osteogenesis and enhance bone volume. Clinical studies and case reports exemplify successful GBR outcomes, further validating the role of biomaterials in periodontal regeneration.

Bone Grafts³:

Bone grafting is a commonly used approach in periodontal regeneration to stimulate bone regeneration and support periodontal tissue healing. Different types of bone grafts can be utilized, including:

- a. **Autografts:** Bone grafts harvested from the patient's own body, such as from the chin, jaw, or hip. Autografts offer excellent biological compatibility but require an additional surgical site for harvesting.
- b. **Allografts:** Bone grafts obtained from a donor, either cadaveric or synthetic. Allografts provide a scaffold for bone regeneration without the need for a second

surgical site. They can be processed to remove immunogenic components while retaining the bone's natural structure.

- c. **Xenografts:** Bone grafts derived from another species, often bovine or porcine sources. Xenografts are processed to minimize immunogenicity while maintaining the necessary biological properties for bone regeneration.
- d. **Alloplastic Bone Substitute Materials:** Synthetic materials such as calcium phosphate ceramics and bioactive glasses are used as bone substitutes. These materials can serve as scaffolds for bone regeneration and can be combined with growth factors for enhanced effects.

Enamel Matrix Derivative (EMD)^{17,18}:

Enamel Matrix Derivative is a protein-based material derived from the enamel matrix of developing teeth. EMD contains various enamel matrix proteins, including amelogenins, enamelin, and ameloblastin, which have shown to have regenerative effects on periodontal tissues. When applied to periodontal defects, EMD promotes the regeneration of cementum, periodontal ligament, and bone, leading to improved periodontal attachment and reduced pocket depths.

Platelet-Derived Growth Factors (PDGF)¹⁹:

Platelet-Derived Growth Factors are growth factors obtained from the patient's own blood platelets. These growth factors play a crucial role in tissue repair and regeneration by stimulating cell migration, proliferation, and differentiation. In periodontal regeneration, PDGF can be applied to the affected area to enhance the regeneration of periodontal tissues, including cementum, periodontal ligament, and bone.

Emerging Nano-Technological Approaches⁸:

Nanotechnology has emerged as a promising field in periodontal regeneration due to its unique properties at the nanoscale. Some of the emerging nano- technological approaches for periodontal regeneration include:

1. **Nanofibers and Nanoscaffolds:** Electrospinning techniques can produce nanofibrous scaffolds with a structure similar to the extracellular matrix. These nanoscaffolds provide a high surface area and can mimic the natural tissue architecture, promoting cell adhesion, proliferation, and differentiation.
2. **Nanoparticles for Drug Delivery:** Nanoparticles can be loaded with growth factors, antimicrobial agents, or other bioactive molecules. These nanoparticles can be designed to release the cargo slowly and in a controlled manner, providing sustained effects to promote tissue regeneration and combat infection.
3. **Nanostructured Coatings:** Nanostructured coatings on dental implants or other biomaterials can improve their biocompatibility and osseointegration. These coatings may incorporate bioactive molecules to stimulate tissue regeneration and prevent bacterial colonization.

4. **Nanoengineered Growth Factors:** Nano-encapsulation of growth factors can protect them from degradation and improve their stability. Furthermore, nanoscale presentation of growth factors can enhance their bioactivity and receptor binding, promoting better tissue regeneration.
5. **Nanotechnology-Enhanced Imaging:** Nanotechnology-based imaging techniques, such as quantum dots and nanosensors, can enable better visualization of periodontal tissues, allowing for more accurate diagnosis and monitoring of regeneration progress.

Nano-Innovations in Periodontics

Nanomaterials for enhanced drug delivery²⁰

Nano-innovations have facilitated the development of nanomaterials for targeted and controlled drug delivery in periodontal treatments. Figure 7 presents a nanocarrier delivering antimicrobial agents to periodontal pockets.²¹ Nanoparticles, liposomes, and other nanocarriers have demonstrated improved drug bioavailability and reduced side effects. Studies exploring the use of nanomaterials to deliver antibiotics, anti-inflammatory agents, and growth factors highlight their potential in combating periodontal diseases effectively.

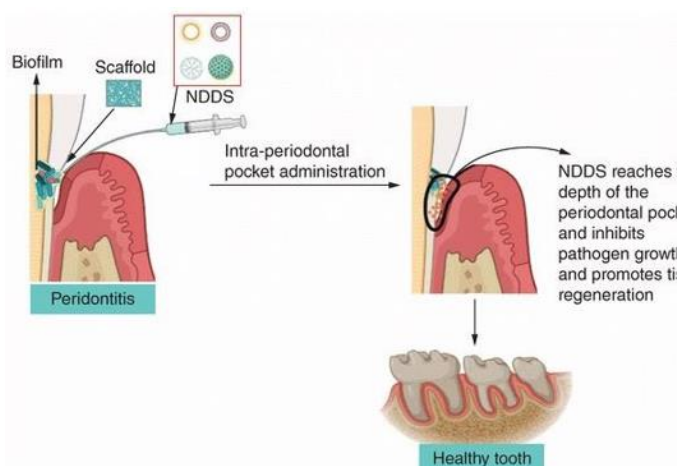


Figure 7: Nanomaterials for enhanced drug delivery²¹

Nanotechnology in tissue engineering

The integration of nanotechnology in tissue engineering has led to the creation of innovative scaffolds and matrices with nanoscale features. Figure 5 showcases a nanofibrous scaffold supporting cell attachment and proliferation. Nanotopography and nanomaterials influence cell behavior, directing cell differentiation and tissue regeneration. This section presents cutting-edge research on nano-engineered scaffolds for periodontal regeneration, emphasizing their ability to guide the formation of functional periodontal tissues.

Advantages and Limitations

The application of pioneering biomaterials and nano-innovations in periodontics offers several advantages, such as enhanced tissue regeneration, minimally invasive procedures, and improved prosthetic success. However, it is crucial to address the current limitations and challenges, including biocompatibility concerns, long-term stability, and accessibility of advanced technologies.

Discussion

The periodontium encompasses the specialized tissues surrounding and supporting teeth within the maxillary and mandibular bones.^{22,23} Tooth loss can result from trauma or various periodontal conditions such as gingivitis, periodontitis, or tissue decay. Periodontal tissue engineering aims to restore the tooth's supporting structures using appropriate biomaterials that stimulate cells and signaling molecules to generate new healthy tissue. Over the past decade, significant progress has been made in regenerating complex periodontal and alveolar bone defects.

Research efforts have focused on polymeric and ceramic scaffolding systems for cell, protein, drug, and gene delivery, leading to the creation of complex and often multifunctional implants with predictable responses. However, there is ongoing debate within the research community regarding the optimal treatment modality for achieving periodontal regeneration. Some advocate for bone replacement grafts alone, while others propose guided tissue membrane (GTR) alone, and still others recommend a combination of both.

A study by Tobon et al.²⁴ compared three treatment modalities for periodontal regeneration and GTR after endodontic surgery. The results indicated that the combination of both membrane and bone graft yielded the best periodontal regeneration, while the control group without membrane or graft showed the worst results. Similarly, studies comparing different types of membranes, such as non-resorbable ePTFE, resorbable PLGA, and resorbable collagen membrane, have yielded diverse outcomes.

Case Studies and Clinical Trials

Clinical studies and case reports have provided compelling evidence of the success of regenerative therapies, exemplifying the potential of biomaterials and nano-innovations in achieving positive outcomes and restoring oral health in patients with periodontal diseases.

Future Perspectives and Emerging Trends

Looking to the future, the Periodontal Renaissance opens up a myriad of opportunities for advancing periodontal care. Personalized regenerative treatments, gene therapy applications, and the integration of artificial intelligence in treatment planning are among the emerging trends that hold tremendous potential for further enhancing the effectiveness and accessibility of regenerative therapies.

Conclusion

The Periodontal Renaissance, characterized by pioneering biomaterials and nano-innovations, has propelled the field of periodontics into a new era of regenerative excellence. The integration of these cutting-edge approaches has the potential to revolutionize periodontal care, leading to improved patient outcomes and a higher quality of life. By harnessing the power of biomaterials and nanotechnology, dental professionals can advance the field of periodontics and provide patients with more effective and personalized regenerative treatments. The future of periodontics is undoubtedly bright, and ongoing research will continue to shape the landscape of periodontal care for years to come.

Source of Funding

None.

Conflict of Interest

None.

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