Recent Advances In Periodontal Regeneration Therapies: A Comprehensive Review

[1] Dr. Uma Sudhakar,[2] S.Bhuvanesh,[3] T.Aswini,[4] Ayesha Mohideen,[5] Ayesha sherin,[6] Bharathi
[1] professor, Head of the department of periodontics ans and implantology.
[2][3][4][5][6] CRRI .

To access & cite this article

Website: tmjpds.com

ABSTRACT

Traditional treatment approaches have primarily focused on symptom control and slowing disease progression. However, recent strides in periodontal regeneration therapies offer promising avenues for reinstating lost periodontal tissues. This comprehensive review undertakes a thorough examination of the most recent advancements in periodontal regeneration treatments, encompassing diverse methodologies like tissue engineering, biomaterials, growth factors, and emerging technologies. Through an exploration of the current status of the field, this review aims to illuminate the potential of these innovative therapies to transform periodontal healthcare and enhance patient outcomes.

Keywords: Periodontal diseases, periodontal regeneration therapies, lost periodontal tissues, in-depth analysis, latest developments.

INTRODUCTION

Periodontal diseases, a broad spectrum of oral health conditions encompassing gingivitis and periodontitis, stand as a formidable public health challenge, affecting a substantial portion of the global population. Inflammatory disorders affecting the gums, alveolar bone, and periodontal ligament are the initial symptoms of these ailments, which eventually lead to tooth loss if left untreated.While conventional treatment modalities have historically centered on managing symptoms and mitigating disease progression, the emergence of recent advancements in periodontal regeneration therapies heralds a transformative era in periodontal care. In the past, the management of periodontal diseases primarily revolved in the vicinity of non-surgical procedures like debridement and root planning, along with surgical procedures like flap surgery and bone grafting. While these approaches have yielded significant improvements in patient outcomes, they often fall short in achieving complete and lasting periodontal tissue regeneration.1 The limitations of these traditional treatments underscore the pressing need for innovative solutions that can restore damaged periodontal tissues to their natural form and function. This review article embarks on a comprehensive exploration of the latest developments in the field of periodontal regeneration therapies. These advancements encompass a diverse array of approaches, including tissue engineering, the utilization of biomaterials, harnessing the potential of growth factors, and leveraging cutting-edge emerging technologies.2 By delving into the current state of research and clinical applications, this review aspires to illuminate the promising potential of these innovative therapies to revolutionize periodontal care, ultimately leading to improved patient outcomes and enhanced oral health.

PERIODONTAL TISSUE DEVELOPMENT

The process of developing periodontal tissue is complex and includes building different supporting structures for the teeth. The dental papilla gives rise to odontoblasts and dental pulp, whereas the dental follicle forms the cementum, periodontal ligament (PDL), and alveolar bone, which are the main constituents of the periodontium.3 Developing simultaneously with the tooth roots, these tissues originate in dental follicles, which are in turn derived from the neural crest. The outside surface of the enamel organ and the dental papilla are close to a unique layer of cells that make up the dental follicle. The perifollicular mesenchyme, a loosely organized cluster of cells that surrounds the tooth bud, is the second major constituent. A natural cleavage plane is created when these strata are separated by a less densely packed area of connective tissue. The primary function of the perifollicular mesenchyme and related bone trabeculae is to support the teeth. Gingiva, cellular cementum covering the apical root, acellular cementum covering the cervical root, PDL rich in blood vessels and stem cells, and lamellar alveolar bone are all parts of the periodontium.4 The complexity of the periodontal regeneration process escalates with the maturation of the tooth due to the specialized microenvironment required for tissue formation. Research has been dedicated to the development of tissue engineering techniques and the replication of specialized microenvironments with the goal of restoring functional periodontal tissues. It is worth mentioning that specific investigations into regenerative endodontics have observed the development of tissue resembling pulp tissue within root canals, in contrast to the regeneration of pulp tissue. During root canal therapy, this may be the result of apical papilla cell migration or PDL stem cell influx.5 In order to tackle this issue, it is imperative to incorporate elements that facilitate the differentiation of stem/progenitor cells and bolster regenerative microenvironments. The restoration of periodontal tissue necessitates the control of regional infections, the mitigation of inflammation, and the creation of a regenerative milieu. In tissue engineering, the design of scaffolds and the selection of appropriate biomaterials for scaffolds are two crucial components. Furthermore, stringent control must be exercised over the release of regulatory molecules, including antimicrobial and anti-inflammatory chemicals and growth factors. To ensure successful regeneration of mineralized (alveolar bone and cementum) and soft (gingiva and PDL) tissues, it is necessary to consider specific biological cues, tissue-specific guiding platforms, and stem cells.

Factors Influencing Periodontal Tissue Engineering

Enamel Matrix Derivative, or EMD

Enamel matrix derivative (EMD) is a biologic substance that has been approved by the FDA for use in periodontal regeneration. It is a mixture of enamel matrix proteins made from swine embryonic dental enamel and propylene glycol alginate. It has been shown that EMD encourages the development of cementum-like stiff tissue, albeit it is still unclear how precisely it works. In vitro, EMD has been demonstrated to produce a variety of effects, including differentiation, angiogenesis, elevated gene

expression, protein synthesis, and suppression of epithelial proliferation. Clinical research supports its use in deep intrabony periodontal problems and root covering treatments. Furthermore, it has demonstrated promise in the management of peri-implantitis by promoting bone growth and reducing the number of pathogenic microbes. To fully explore the possibilities of this approach in the context of sinus floor augmentation, peri-implant defect, and alveolar ridge augmentation, more research is necessary.6

rh-PDGF-BB, also known as recombinant human platelet-derived growth factor-BB

In periodontal tissue engineering, rh-PDGF-BB, a well-studied growth factor, is employed. This material, which is sold commercially as GEM 21S, has a substantially higher concentration of PDGF than both growth factor-rich plasma (PRGF) and platelet-rich plasma (PRP). Periodontal ligament (PDL) cells and mesenchymal stem cells (MSCs) are two examples of the many cell types on which PDGF-BB is known to have mitogenic and chemotactic effects. Collagen, glycosaminoglycan, chemotaxis, and fibroblast DNA synthesis have all been demonstrated to be enhanced by it.

Studies have indicated that in preclinical and clinical contexts, rh-PDGF-BB causes increased lateral bone growth, clinical attachment gain, and decreased probing depth.Additionally, it has shown effective in GBR processes. More study is required in this field as the usage of it for root covering treatments has produced variable outcomes.7 Fibroblast Growth Factor-2 (FGF-2):

Also referred to as basic fibroblast growth factor, FGF-2 is an essential component of angiogenesis, wound healing, tissue remodeling, and cell division. For maximum bioactivity, heparin or heparin sulfates are needed. FGF-2 has been utilized in guided bone regeneration (GBR), implant osseointegration, peri-implant defects, and intrabony periodontal abnormalities by periodontal tissue engineering. Clinical studies have demonstrated a substantial increase in bone fill when FGF-2 is used to correct intrabony abnormalities. Effects that are dose-dependent have been noted, with some doses showing greater effectiveness. Additionally, FGF-2 has shown promise in advancing osseointegration in implants with inadequate primary stability. Preclinical research has investigated the synergistic effects of FGF-2 in conjunction with other growth factors, like BMP-2, to promote bone formation.8

ADVANCED MANUFACTURING TECHNIQUES FOR PERSONALIZED PERIODONTAL TISSUE REGENERATION

Utilizing additive manufacturing (AM) techniques like fused deposition modeling (FDM) and selective laser sintering (SLS), scaffolds for periodontal tissue regeneration that are tailored to individual patients have been manufactured. Nonetheless, these constructs produced via FDM and SLS are frequently cumbersome and may impede tissue ingrowth and stability.9 In an effort to address these constraints, contemporary research has been devoted to the development of biomimetic scaffolds that mimic the extracellular matrix (ECM) microenvironment and are nanofibrous and multiphasic. Electrospinning and other nanofibrous scaffolding techniques provide an environment resembling extracellular matrix (ECM), which stimulates fibroblast proliferation and the upregulation of periodontal ligament (PDL)-specific biomarkers. The elongation of cells and the orientation of collagen fibers on the scaffold surface are directed by aligned electrospun fibers. It has been demonstrated that a biodegradable nanofibrous mat-based 3D multilayered scaffold comprised of precisely aligned nanofibrous mats can promote periodontal tissue regeneration. Conversely, the lack of patient-specific geometries and densely packed fibrous structures in electrospun scaffolds may impede cellular infiltration. In contrast, the utilization of melt electrospinning writing (MEW) in conjunction with 3D printing provides meticulous regulation of fiber deposition, enabling the fabrication of scaffolds that are geometrically delineated to facilitate periodontal tissue regeneration. The integration of this methodology with image-based processing facilitates the production of customized scaffolds to support anatomically intricate structures. Using MEW, scientists have optimized zonal-specific scaffolds that direct the polarization of macrophages and tissue-specific stem cell differentiation. The scaffolds' fiber alignment facilitates the polarization of pro-healing macrophages and increases the expression of ligamentogenic markers; conversely, the spacing of fibers affects the expression of osteogenic markers.10 Research conducted in vivo using a periodontal fenestration defect model has illustrated the capacity of MEW to regulate the regeneration of soft (PDL) and hard (alveolar bone and cementum) tissues along the tooth root. MEW may be utilized to fabricate personalized scaffolds at the clinical scale and with high printing accuracy for regenerative periodontics, according to these results.11

Architectural scaffolds for periodontial tissue regeneration

New developments in tissue engineering have given rise to different scaffold approaches for the regeneration of periodontal tissue.12 These methods include cell sheets, decellularized extracellular matrix (ECM), injectable scaffolds, prefabricated porous scaffolds, and cell encapsulation in hydrogels that self-assemble. They also include fast prototyping. To provide a 3D environment for tissue repair and regeneration, the decellularized extracellular matrix (ECM) is frequently utilized, as it closely resembles the properties of the natural ECM. Tissue engineering makes extensive use of prefabricated porous scaffolds, both synthetic and natural. The interconnected and highly porous 3D scaffolds offer the perfect setting for interactions between cells and scaffolds.13. Enhancing tissue integration at the implantation site, they can be customized to match the characteristics of the natural extracellular matrix. There are two types of scaffolds: pre-formed and injectable. Injectable scaffolds have the advantage of being easier to apply, more versatile in filling defects that are orientated randomly, and able to address issues with cell adhesion and fixation. Moreover, bioactive compounds can be transported via injectable scaffolds to support regeneration.

Scaffolds may be monophasic or multiphasic depending on their composition. Monophasic scaffolds, often created through electrospinning, maintain consistent physical and chemical properties.14 Multiphasic scaffolds involve multiple materials, each guiding the regeneration of different tissues. Technologies like 3D printing offer design freedom and can produce both monophasic and multiphasic scaffolds. The interoperability of 3D printing with diagnostic tools like cone beam computed tomography and intraoral 3D scanners further enhances its utility. When it comes to periodontal ligament (PDL) regeneration, the alignment of PDL fibers is crucial.15 Various methods have been explored, including electrospinning for fiber alignment and the creation of channel-containing scaffolds. However, challenges remain in achieving precise fiber alignment. Mechanical stress on aligned scaffolds can aid in PDL-like tissue formation, highlighting the importance of functional regeneration. Nanotechnology and nanomaterials show promise in periodontal disease care, offering the potential for precise control and delivery of therapeutic agents at nano, micro, and macro scales. Ongoing research in nanotechnology is expected to further advance these possibilities.16

ADVANCES IN GUIDED TISSUE REGENERATION (GTR) MEMBRANES FOR PERIODONTAL THERAPY

In order to support the regeneration of the periodontal ligament (PDL) and alveolar bone, barrier membranes for guided tissue regeneration (GTR) are essential because they inhibit epithelial cell ingrowth and make space for it. These fundamental features, together with biocompatibility, tissue integration, cell occlusiveness, space maintenance, and clinical manageability, should be present in these membranes. Absorbable and non-absorbable GTR barrier membranes are the two main classifications. Non-absorbing membranes like Gore-tex® (polytetrafluoroethylene; PTFE), provide enhanced space maintenance. However, their removal necessitates a subsequent surgical procedure, which escalates the potential for infection and hinders regenerative results.18,19 The incorporation of titanium into PTFE membranes improves their mechanical properties and tissue compatibility. As absorbable membranes, on the other hand, degrade progressively within the body, a second operation is unnecessary.20 Natural biomaterials possess mechanical strength and biocompatibility, whereas synthetic biomaterials feature mechanical properties and tunable degradation rates, but do not incorporate cellular binding motifs. It is essential to achieve a balance in the rate of degradation in order to preserve space and encourage tissue formation. New functionalities and the enhancement of mechanical and degradation properties have been the focus of recent advancements in GTR membranes. By combining natural and synthetic polymers, composite membranes hope to combine biorecognition with increased mechanical strength. Antibacterial agents are also transported via GTR membranes, where they inhibit local inflammation and infection while promoting the formation of PDL tissue. The purpose of designing multilayered membranes with distinct functions in each layer is to enhance the regeneration of periodontal tissue. The majority of GTR membranes are still in the experimental phase, requiring additional in vivo research and clinical trials to evaluate their safety and effectiveness, despite these developments. Given the inherent unpredictability of treatment outcomes for diverse periodontal defects, the integration of GTR membranes with additional modalities, such as bone grafts, might potentially yield more favorable regenerative outcomes.21

LASER THERAPY IN PERIODONTAL REGENERATION

The origin of the word "laser" can be traced back to the acronym LASER, which represents "light amplification by stimulated emission of radiation." Laser therapy has garnered considerable attention for more than twenty years on account of its alleged benefits, which include soft tissue ablation, bactericidal activity, and hemostasis enhancement.22 It has been documented that low-power laser irradiation can induce cellular processes including differentiation, migration, and proliferation. Nevertheless, the conventional notion that lasers deliver superior clinical results in comparison to traditional scaling and root planing (SRP) alone for a period of 24 months following treatment has been called into question by recent reviews.23 Despite being compared to other debridement methods and conventional surgical procedures such as open flap debridement (OFD), lasers do not appear to provide any substantial additional advantages. Two significant human histologic investigations have utilized a particular minimally invasive protocol in conjunction with the short-wavelength neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.24 The protocol involves the utilization of a pulsed Nd: YAG laser to eliminate pocket epithelium, followed by a second lasering of the pockets to ostensibly encapsulate the pocket and stabilize blood clots. Significantly, the aforementioned studies documented possible regenerative impacts of laser therapy.25 Three months following laser treatment, Yukna et al. observed the development of functional connective tissue attachment, bone, and new cementum in intrabony spaces. In contrast, control defects that were exclusively treated with SRP exhibited long junctional epithelium and periodontal repair.26 Likewise, histological findings of diverse levels of periodontal regeneration, such as the development of fresh cementum, periodontal ligament, and alveolar bone, were documented by Nevins et al. on ten teeth obtained from eight patients as a result of laser therapy.27

ELECTROSPUN NANOFIBERS FOR ADVANCED PERIODONTAL REGENERATION

Tissue-engineered scaffolds have been essential to the regeneration of periodontal tissue in recent years. In addition to natural polymers like chitosan, gelatin, and collagen, these scaffolds are made of synthetic polymers like PCL, PLA, PLGA, and PEG. Although their structural characteristics can be altered, synthetic polymers might not have any biological function. Natural polymers, on the other hand, provide superior matrix formation, cell adhesion, and proliferation along with outstanding biocompatibility. Scaffolds with the advantages of both natural and synthetic polymers can be produced by combining them. Because of its special qualities, such as their high surface area-to-volume ratio, porosity, and interconnectivity, nanofibrous scaffolds have attracted interest. These characteristics resemble those of the extracellular matrix (ECM), promoting cell adhesion, proliferation, and nutrition exchange. A low-cost method for creating continuous fibers with dimensions between nanometers and micrometers is electrospinning. The fiber's diameter, orientation, porosity, and surface features can all be precisely controlled with this process. A metallic spinneret, a grounded collector, a high-voltage power supply, and a syringe filled with a polymeric solution are the basic components of the electrospinning setup. The method is based on the electrostatic forces that cause the charged polymeric solution's droplets to lengthen into fibers. The solvent subsequently evaporates, causing the fibers to harden and create non-woven fibrous membranes. The characteristics of electrospun fibers are determined by a multitude of elements that can be divided into three categories: solution, process, and ambient conditions. These variables include temperature, humidity, needle diameter, needle-to-collector distance, voltage, flow velocity, viscosity, surface tension, and concentration of the solution.28 Scaffolds made of electrospun nanofibrous material are ideal for periodontal tissue engineering. Their small pore size and high porosity make them perfect for barrier membranes used in guided tissue regeneration (GTR). GTR membranes support periodontal regeneration and inhibit undesirable cell movement over the scaffold. Ideal GTR membranes that are osteoinductive, biodegradable, biocompatible, and mechanically strong can be produced by carefully choosing polymers and fine-tuning electrospinning settings. Furthermore, to improve their biological effects, these scaffolds can be functionalized with a variety of additions, including ceramics, growth factors, antibiotics, and small compounds. For example, adding hydroxyapatite improves osteoconductivity and bioactivity while simulating the composition of natural bone. Scaffolds can also be engineered to encourage stem cell differentiation and facilitate tissue-specific regeneration, such as that of the periodontal ligament, cementum, and bone. Although electrospun nanofibers have been the subject of numerous in vitro and in vivo investigations for periodontal regeneration, clinical trials are still in their early phases. However, the trials' results are

encouraging, indicating that patients treated with electrospun scaffolds had better tooth attachment, lower probing depths, and less periodontal inflammation. This suggests that these sophisticated scaffolds could be useful substitutes for periodontal treatment.29

GENE THERAPY FOR ENHANCED TISSUE REGENERATION

To achieve tissue regeneration, it is essential that growth factors be utilized to stimulate specific and precise cellular signals. Nevertheless, the efficient administration of these growth factors may prove to be a formidable task owing to their relatively brief half-lives and propensity to disseminate into adjacent tissues. As an illustration, PDGF-BB exhibited a half-life of merely 4.2 hours in a porcine model, culminating in 96% clearance taking place within 96 hours.30 The conventional approach to topically administering growth factors, often involving a single high-dose administration, has this inherent limitation. Such a method may result in a rapid burst release, potentially impeding the bioactivity of other growth factors. Because gene therapy can continue to produce and secrete growth factors, it presents a potentially viable answer to these challenges. This tactic creates and releases growth factors continuously by using gene therapy to alter cells. This methodology has several advantages, including the production of proteins with authentic post-translational modifications and heightened biological activity. Gene therapy utilizes a wide range of vectors, including lentiviruses, baculoviruses, plasmids, adenoviruses (Ad), retroviruses, and adeno-associated viruses (AAVs), each with unique advantages and disadvantages.. As an illustration, a preclinical model was utilized in a study conducted by Dunn et al. to treat peri-implant osseous defects with Ad-BMP-7 delivered via collagen matrix. On the first day, this gene therapy strategy commenced gene delivery, and by the fourth day, expression had peaked. Enhanced new bone-to-implant contact, improved alveolar bone defect fill, and increased coronal new bone formation were observed in the vicinity of dental implant fixtures. In an effort to mitigate apprehensions regarding the cytotoxicity, host immunogenicity, and viral transduction rates associated with high viral dosages, scholars have investigated the possibility of embedding or attaching gene therapy vectors to materials. This methodology presents a highly auspicious foundation for sustained and localized gene delivery. As an illustration, Hao et al. devised a dual-gene therapy delivery system by employing chemical vapor deposition on surfaces of FDA-approved biomaterials such as titanium, PCL, and PLGA. This system deployed successfully. The delivery of BMP-7 and PDGF-B gene vectors to human periodontal ligament (PDL) cells led to sustained and localized protein synthesis, with highest levels of expression observed between days 7 and 10, in contrast to the process of direct physical absorption.31.

DISCUSSION

This comprehensive review article delves deeply into the multifaceted realm of periodontal regeneration therapies, addressing the significant global public health challenge posed by periodontal diseases. It underscores the historical focus on symptom management and disease progression mitigation in conventional treatments, drawing attention to their inherent limitations in achieving complete and enduring periodontal tissue regeneration. The article begins by elucidating the intricate process of periodontal tissue development, emphasizing the specialized microenvironment required for tissue formation. It then delves into the pivotal role of growth factors, such as Enamel Matrix Derivative (EMD), Recombinant Human Platelet-Derived Growth Factor-BB (rh-PDGF-BB), and Fibroblast Growth Factor-2 (FGF-2), in stimulating tissue regeneration and their diverse applications in clinical settings. The exploration extends to advanced manufacturing techniques, particularly 3D printing and electrospinning, which empower the creation of personalized, anatomically precise scaffolds to facilitate periodontal tissue regeneration. The discussion on scaffold architectures highlights the significance of scaffold properties and their suitability for specific regenerative purposes. Additionally, the potential of nanotechnology to further enhance periodontal regeneration is briefly mentioned. Guided Tissue Regeneration (GTR) membranes emerge as crucial tools in establishing an environment conducive to periodontal tissue regeneration, where non-absorbable and absorbable membranes play distinct roles, and ongoing research seeks to optimize their mechanical and degradation properties. The article also broaches the debate on the efficacy of laser therapy compared to traditional treatments, presenting both supportive and opposing viewpoints, with mention of specific laser protocols that have shown regenerative potential. Electrospun nanofibers, with their remarkable properties, are recognized as promising for periodontal tissue engineering, as they mimic the extracellular matrix and can be customized for guided tissue regeneration. The review also emphasizes the need for further clinical trials to solidify their potential as effective alternatives in periodontal therapy. Finally, gene therapy is

introduced as a cutting-edge approach to overcome challenges associated with the delivery of growth factors, enabling sustained and localized synthesis and secretion. The article touches on various vectors and strategies, showcasing the potential to revolutionize periodontal regeneration therapies. In conclusion, the comprehensive exploration of these advanced therapies illustrates their promising potential to transform periodontal care and elevate patient outcomes, underlining the significance of continued research and clinical validation.

CONCLUSION

In the realm of periodontal regeneration, there is still much to learn despite tremendous advancements. To improve these treatments, streamline their delivery, and evaluate their long-term effects, more study is required. Additionally, investigating their potential applications in sinus floor augmentation and alveolar ridge augmentation holds promise for addressing a broader range of clinical challenges. In summary, the recent advances in periodontal regeneration therapies offer hope for more effective and less invasive treatments for individuals suffering from periodontal diseases. As research continues to evolve and clinical applications expand, these therapies have the potential to significantly improve the quality of life for patients and redefine the standards of periodontal care.

REFERENCES:

1. Cho, M.-I., & Garant, P. R. (2000). Development and general structure of the periodontium. *Periodontology 2000*, 24(1), 9–27.
2. Xiong, J., Gronthos, S., & Bartold, P. M. (2013). Role of the epithelial cell rests of Malassez in the development, maintenance and regeneration of periodontal ligament tissues. *Periodontology 2000*, 63(1), 217–233
3. Verma, Nitin Kumar; Ompal, Sangeeta Singh; Prakash, Priyanka; Mukherjee, Manish; Jha, A K. Recent advances in materials for periodontal regeneration. Journal of Dentistry Defence Section 15(2):p 130-139, Jul–Dec 2021. | DOI: 10.4103/JODD.JODD_44_20
4. Dangaria, S. J., Ito, Y., Luan, X., & Diekwisch, T. G. H. (2011). Successful periodontal ligament regeneration by periodontal progenitor preseeding on natural tooth root surfaces. *Stem Cells and Development*, 20(10), 1659–1668.
5. Eke, P. I., Dye, B. A., Wei, L., Slade, G. D., Thornton-Evans, G. O., Borgnakke, W. S., … Genco, R. J. (2015). Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *Journal of Periodontology*, 86(5), 611–622.
6. Galli M, Yao Y, Giannobile WV, Wang HL. Current and future trends in periodontal tissue engineering and bone regeneration. Plastic and Aesthetic Research. 2021; 8: 3.
7. Darby IB, Morris KH. A systematic review of the use of growth factors in human periodontal regeneration. J Periodontol 2013;84:465-76.
8. Lin Z, Rios HF, Cochran DL. Emerging regenerative approaches for periodontal reconstruction: a systematic review from the AAP Regeneration Workshop. J Periodontol 2015;86:S134-52.
9. Daghrery, A., Aytac, Z., Dubey, N., Mei, L., Schwendeman, A., & Bottino, M. C. (2020). Electrospinning of dexamethasone/cyclodextrin inclusion complex polymer fibers for dental pulp therapy. *Colloids and Surfaces B: Biointerfaces*,
10. Daghrery, A., de Souza Araújo, I. J., Castilho, M., Malda, J., & Bottino, M. C. (2022). Unveiling the potential of melt electrowriting in regenerative dental medicine. *Acta Biomaterialia*.
11. Daghrery, A., Ferreira, J. A., de Souza Araújo, I. J., Clarkson, B. H., Eckert, G. J., Bhaduri, S. B., … Bottino, M. C. (2021). A highly ordered, nanostructured fluorinated CaP-coated melt electrowritten scaffold for periodontal tissue regeneration. *Advanced Healthcare Materials*, 10, e2101152.
12. Mariyam Sheikh, Prasad Dhadse, Recent Advances in Scaffolds for Periodontal Regeneration, J Res Med Dent Sci, 2022, 10 (10): 260-264.
13. Yamada S, Shanbhag S, Mustafa K. Scaffolds in Periodontal Regenerative Treatment. Dent Clin North Am 2021; 66:111-130.
14. Jiang W, Li L, Zhang D, et al. Incorporation of aligned PCL–PEG nanoϭibers into porous chitosan scaffolds improved the orientation of collagen ϭibers in regenerated periodontium. Acta biomaterialia 2015; 25:240-252.
15. Park CH, Rios HF, Jin Q, et al. Tissue engineering bone-ligament complexes using ϭibreĞguiding scaffolds. Biomaterials 2012; 33:137-145
16. Liang Y, Luan X, Liu X. Recent advances in periodontal regeneration: A biomaterial perspective. Bioact Mater. 2020 Feb 28;5(2):297-308. doi: 10.1016/j.bioactmat.2020.02.012. PMID: 32154444; PMCID: PMC7052441.

17. Sam G., Baiju R.M. Evolution of barrier membranes in periodontal Regeneration-"Are the third generation membranes really here? 2014;8 ZE14-Z17.
18. Li M, Lv J, Yang Y, Cheng G, Guo S, Liu C, Ding Y. Advances of Hydrogel Therapy in Periodontal Regeneration—A Materials Perspective Review. *Gels*. 2022; 8(10):624.
19. Chen, F.M.; Jin, Y. Periodontal tissue engineering and regeneration: Current approaches and expanding opportunities. Tissue Eng. Part B Rev. 2010, 16, 219–255.
20. Chen, X.; Wu, G.; Feng, Z.; Dong, Y.; Zhou, W.; Li, B.; Bai, S.; Zhao, Y. Advanced biomaterials and their potential applications in the treatment of periodontal disease. Crit. Rev. Biotechnol. 2016, 36, 760–775.
21. Liu, J.; Ruan, J.; Weir, M.D.; Ren, K.; Schneider, A.; Wang, P.; Oates, T.W.; Chang, X.; Xu, H.H.K. Periodontal Bone-Ligament-Cementum Regeneration via Scaffolds and Stem Cells. Cells 2019, 8, 537.
22. Yuan, W.; Wang, H.; Fang, C.; Yang, Y.; Xia, X.; Yang, B.; Lin, Y.; Li, G.; Bian, L. Microscopic local stiffening in a supramolecular hydrogel network expedites stem cell mechanosensing in 3D and bone regeneration. Mater. Horiz. 2021, 8, 1722–1734.
23. Zang, S.; Mu, R.; Chen, F.; Wei, X.; Zhu, L.; Han, B.; Yu, H.; Bi, B.; Chen, B.; Wang, Q.; et al. Injectable chitosan/β-glycerophosphate hydrogels with sustained release of BMP-7 and ornidazole in periodontal wound healing of class III furcation defects. Mater. Sci. Eng. C Mater. Biol. Appl. 2019, 99, 919–928.
24. Pan, J.; Deng, J.; Yu, L.; Wang, Y.; Zhang, W.; Han, X.; Camargo, P.H.C.; Wang, J.; Liu, Y. Investigating the repair of alveolar bone defects by gelatin methacrylate hydrogels-encapsulated human periodontal ligament stem cells. J. Mater. Sci. Mater. Med. 2019, 31, 3.
25. Momose, T.; Miyaji, H.; Kato, A.; Ogawa, K.; Yoshida, T.; Nishida, E.; Murakami, S.; Kosen, Y.; Sugaya, T.; Kawanami, M. Collagen Hydrogel Scaffold and Fibroblast Growth Factor-2 Accelerate Periodontal Healing of Class II Furcation Defects in Dog. Open Dent. J. 2016, 10, 347–359Kreller, T.; Distler, T.; Heid,
26. S.; Gerth, S.; Detsch, R.; Boccaccini, A.R. Physico-chemical modification of gelatine for the improvement of 3D printability of oxidized alginate-gelatine hydrogels towards cartilage tissue engineering. Mater. Des. 2021, 208, 109877.
27. Wu JY, Chen CH, Yeh LY, Yeh ML, Ting CC, Wang YH. Low-power laser irradiation promotes the proliferation and osteogenic differentiation of human periodontal ligament cells via cyclic adenosine monophosphate Int J Oral Sci. 2013;5:85–91
28. Schwarz F, Aoki A, Becker J, Sculean A. Laser application in non-surgical periodontal therapy: A systematic review J Clin Periodontol. 2008;35:29–44
29. Santos MS, Carvalho MS, Silva JC. Recent Advances on Electrospun Nanofibers for Periodontal Regeneration. *Nanomaterials*. 2023; 13(8):1307.
30. Vaquette C, Pilipchuk SP, Bartold PM, Hutmacher DW, Giannobile WV, Ivanovski S. Tissue engineered constructs for periodontal regeneration: current status and future perspectives. *Adv Healthc Mater* 2018;7:e1800457.
31. Moreno Sancho F, Leira Y, Orlandi M, Buti J, Giannobile WV, D'Aiuto F. Cell-based therapies for alveolar bone and periodontal regeneration: concise review. *Stem Cells Transl Med* 2019;8:1286-95.