Medical Science

To Cite:
Cybulska K, Janczarski S, Banaszczyk J, Górski E, Papierz J, Królczyk G, Pietrzyk A, Krajewski M. Next-Generation Periodontal Regeneration: Bridging Biologically Driven Therapies and Tissue Engineering – A Literature Review. *Medical Science* 2026; 30: e159ms3957
doi:

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Peer-Review History
Received: 16 February 2026
Reviewed & Revised: 07/March/2026 to 15/July/2026
Accepted: 29 July 2026
Published: 23 August 2026

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Next-Generation Periodontal Regeneration: Bridging Biologically Driven Therapies and Tissue Engineering – A Literature Review

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ABSTRACT

The article presents the clinical transformation of periodontal regeneration therapy. It offers a unique view on the movement from mechanical methods to cellular signaling and custom three-dimensional tissue engineering techniques. In particular, the review focuses on the apparatus responsible for holding the teeth, namely, the alveolar bone, periodontal ligaments (PDLs), and cementum tissue. Initially, GTR used barrier membranes to block unwanted cells from the healing site, causing varying outcomes. However, in the past two decades, the field of periodontal regeneration has moved from using physical barriers to biological methods and bioengineering techniques. The introduction of biochemical substances, such as EMD, recombinant human growth factors (rhPDGF-BB, rhBMP-2), and platelet concentrates (A-PRF, i-PRF), has enabled faster healing of soft and hard tissues. Furthermore, regenerative medicine has introduced new methods, including cell-based therapies (mesenchymal stem cells from PDLs and dental pulp) and cell-free therapies (exosomes), as well as 3D printing of biomimetic scaffolds that imitate the structure of the periodontium.

Keywords: periodontal regeneration; guided tissue regeneration; enamel matrix derivative; platelet-rich fibrin; stem cells; exosomes; 3D bioprinting; tissue engineering.

1. INTRODUCTION

Periodontitis is a chronic inflammatory condition characterized by the progressive destruction of the tooth-supporting structures, ultimately leading to tooth loss if left unmanaged. The fundamental goal of periodontal therapy has evolved from halting disease progression and managing soft tissue pockets to predictably regenerating the lost insertion apparatus—comprising newly formed alveolar bone, functional perpendicular Sharpey's fibers, and cementum (Gottlow et al., 1986; Cortellini & Tonetti, 2015).

For many years, reactive and reparative procedures were widely used, including open flap debridement that mostly relied on healing through a long junctional

epithelium instead of periodontal regeneration (Gottlow et al., 1986; Kornman & Robertson, 2000). The introduction of the GTR procedure in the 1980s was a landmark because it defined the concept of cell exclusion, using barrier membranes to prevent rapid epithelial cell penetration into the defect site and allowing slower osteogenic and periodontal ligament (PDL) cells to cover the root surfaces (Gottlow et al., 1986; Sculean et al., 2008; Needleman et al., 2006).

However, mechanical barriers had certain drawbacks, including early exposure of the membrane, soft tissue dehiscence, and limited ability to attract cells for regeneration in defects where space was not maintained (Needleman et al., 2006; Susin & Wikesjö, 2013). Due to this challenge, a biological turn in periodontics was developed:

- *Biological signaling*: EMD, rhPDGF-BB, along with different platelet concentrates (L-PRF, A-PRF, i-PRF) were used clinically to promote cell migration, blood vessel formation, and matrix creation (Hammarström, 1997; Nevins et al., 2005; Miron et al., 2017).
- *Advanced Biofabrication*: There's been rapid advancement in stem cell biology (PDLSCs, DPSCs), signaling through exosomes, and additive manufacturing (3D/4D bioprinting of complex scaffolds) that has opened up new possibilities for creating custom anatomically matched constructs that can guide multi-tissue regeneration (Seo et al., 2004; Liu et al., 2022; Raszewski et al., 2024; Sowmya et al., 2017).

This literature review connects the clinical and biological development of periodontal regenerative therapy—tracing the journey from simple mechanical barriers to current biologically oriented protocols and the latest in 3D tissue engineering.

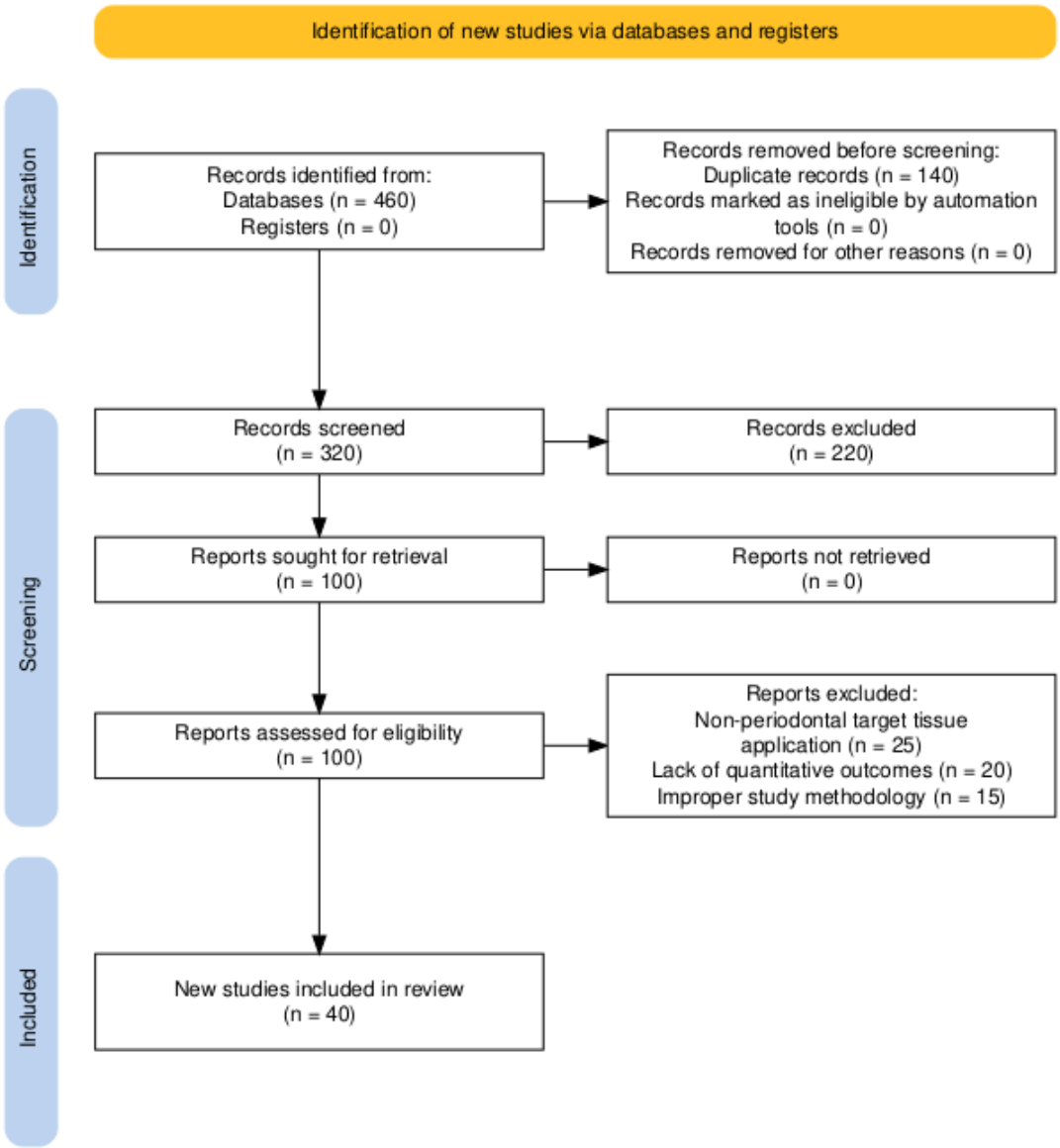

Figure 1. PRISMA 2020 flow diagram illustrating the literature search and selection process.

2. REVIEW METHODS

Periodontal regeneration techniques

The literature search covered all relevant literature up to January 2026 using multiple databases, including PubMed, Scopus, Web of Science, and Google Scholar. The terms used in the search included: Periodontal regeneration, Platelet-rich fibrin, Enamel matrix derivative, rhPDGF-BB, Guided tissue regeneration, Periodontal ligament stem cells, 3D scaffolds, and Exosomes. The search returned 460 articles, which were further filtered from PubMed (n=190), Scopus (n=150), and Web of Science (n=120). Of these, 140 were duplicates. Only studies published in peer-reviewed journals and that attempted to provide physiological and biological mechanisms behind periodontal treatments, along with randomized controlled trials or systematic reviews, were included in the research process. Non-peer-reviewed commentaries and opinion pieces were not included in the research. In addition, the full-text assessment of 100 articles excluded many reports due to non-periodontal target tissue application (25), lack of quantitative outcomes (20), and improper study methodology (15). In total, 40 articles were shortlisted for the final research. The detailed screening and selection workflow following PRISMA guidelines is depicted in Figure 1.

3. RESULTS AND DISCUSSION

Conventional GTR, Foundations and Traditional Surgery: The Era of the Mechanical Exclusion Approach

The biological basis for periodontal regeneration was established by Gottlow and colleagues, showing that when you mechanically separate the gingival connective tissue and epithelium from the tooth surface, it creates a chance for cells from the PDL and alveolar bone to make new attachments (Gottlow et al., 1986). The first type of non-resorbable e-PTFE membranes proved the concept but needed extra surgery for removal, which often ended up damaging the newly formed structures (Sculean et al., 2008; Murphy et al., 2018). Later on, second-generation resorbable synthetic (polylactic/polyglycolic acid) and natural (porcine/bovine collagen) membranes helped avoid those additional surgeries. However, things like early enzymatic breakdown and mechanical pressure from the soft tissue on top became significant issues, especially in treating larger 1- or 2-wall intra-osseous defects (Murphy et al., 2018; Needleman et al., 2006).

To ensure clinical predictability of regenerative procedures, the next step in the development of surgical techniques was to implement a minimally invasive approach. Cortellini and Tonetti (2007) invented the Minimally Invasive Surgical Technique (MIST) and modified MIST (S-MIST) involving micro-instruments and surgical magnification for preservation of interdental papillae and maintenance of local vascularization. The benefits of minimally invasive flaps included improvement of primary wound healing, reduction of flap tension, stabilization of intra-defect fibrin clot formation – essential pre-requisite for effective regeneration irrespective of the type of biomaterial used (Cortellini & Tonetti, 2007; Sanz et al., 2012; Trombelli & Farina, 2008). In numerical terms, the use of micro-surgical MIST procedures resulted in closure of 92-98% of corrected defects with primary flaps, greatly reducing the occurrence of initial wound dehiscence compared to traditional thick flap GTR methods.

Nevertheless, even with these advancements, research, including Cochrane meta-analyses carried out by Needleman et al., shows that the conventional guided tissue regeneration procedure still results in highly unpredictable gain in CAL depending on both surgical technique and defect morphology (Sanz et al., 2012; Needleman et al., 2006; Susin & Wikesjö, 2013). As the meta-analysis data indicate, implementation of GTR provides a statistically meaningful average CAL increase of 1.30 mm to 1.58 mm. At the same time, complications remain high, with membrane exposure ranging from 30% to 50%, which considerably reduces the gain of new bone to under 60%. Thus, the use of bioactive components to regulate cell activity is mandated.

Biologically Driven Regeneration: Signaling Molecules and Blood Concentrates

The trend toward biological procedures started with Enamel Matrix Derivative (EMD), an extract that contains mostly amelogenins (Hammarström, 1997). EMD emulates the physiological processes taking place during tooth root development and stimulates the cementoblasts and periodontal ligament fibroblasts to lay down acellular extrinsic fiber cementum (Hammarström, 1997; Miron et al., 2016). Long-term clinical studies confirmed that EMD provides CAL benefits similar to those achieved with GTR while showing better soft tissue healing and a reduced number of complications (Miron et al., 2016).

At the same time, recombinant human growth factors became available to increase hard tissue formation. The recombinant human platelet-derived growth factor-BB (rhPDGF-BB), in combination with artificial matrix (β-TCP), showed high bone fill and attachment gain in phase III clinical trials due to strong stimulation of cell migration and proliferation (Nevins et al., 2005; Giannobile, 1996). Similar osteoinductive properties were shown by the bone morphogenetic proteins (rhBMP-2, rhBMP-7). However, their clinical

application in periodontics requires strict dosage control to avoid adverse effects such as ankylosis or root resorption (Cochran & Wozney, 1999).

The evolution of autologous blood concentrates also took place. The progression of early Platelet-Rich Plasma (PRP) to the second generation of Platelet-Rich Fibrin (PRF) made it possible to get rid of bovine thrombin and anticoagulants (Choukroun et al., 2006). Further changes in centrifugation settings resulted in advanced PRF (A-PRF) and injectable PRF (i-PRF) based on the Low-Speed Centrifugation Concept (LSCC) (Ghanaati et al., 2014; Miron et al., 2017). Less centrifugal force preserves more leukocytes, macrophages, and platelets that are enclosed in the three-dimensional fibrin clot. Thus, there is a continuous delivery of growth factors (TGF-β1, VEGF, PDGF) during 10-14 days (Ghanaati et al., 2014; Miron & Zhang, 2018). Currently, clinical practice tends to use combinations of bioactive substances (for example, EMD in combination with PRF or bone grafts) (Taraszkiewicz-Sulik et al., 2021).

Cell-Based and Cell-Free Therapies: Stem Cells and Exosomes

As signaling molecules increase tissue responsiveness, defective areas with an insufficient population of resident cells respond well to cell therapy. Human Periodontal Ligament Stem Cells (PDLSCs) were initially isolated by Seo et al., (2004) who showed their pluripotent abilities and potential to form cementum- and periodontal ligament-like structures in vivo. Dental Mesenchymal Stem Cells (D-MSCs), including DPSCs and Stem Cells from Human Exfoliated Deciduous Teeth (SHED), demonstrate excellent proliferating ability and immunomodulatory function (Iwashita et al., 2020; Sharpe, 2016).

To transplant cells without destroying their pericellular ECM, the Cell Sheet Engineering technique has been developed. Cell sheets are obtained by culturing cells on pNIPAAm plates, enabling harvesting of complete cell sheets with cell-cell junctions and matrix proteins intact, which improves cell retention post-transplantation (Iwata et al., 2009). However, despite successful clinical results, the translational use of cell therapies is hindered by strict regulatory control, high production costs due to GMP requirements, and potential problems with cell survival in the ischemic defect microenvironment (Chen et al., 2012; Mao & Prockop, 2012; Nunez et al., 2019).

Such constraints of translational application have encouraged further research into cell-free therapy options. It has been found that regenerative effects of MSCs occur mainly through paracrine action of EVs produced by them, in particular, exosomes (Liu et al., 2022). The cargo of exosomes includes microRNAs, proteins, and lipids with anti-inflammatory, proangiogenic, and pro-stemness actions (Liu et al., 2022; Lei et al., 2021). In contrast to whole-cell transplants, exosome treatments have low immunogenicity, lower malformation risk, simpler storage, and better off-the-shelf therapeutic potential (Lei et al., 2021; Panchenko et al., 2023). The convergence of these cell-based, cell-free, and biofabrication strategies is illustrated in Figure 2.

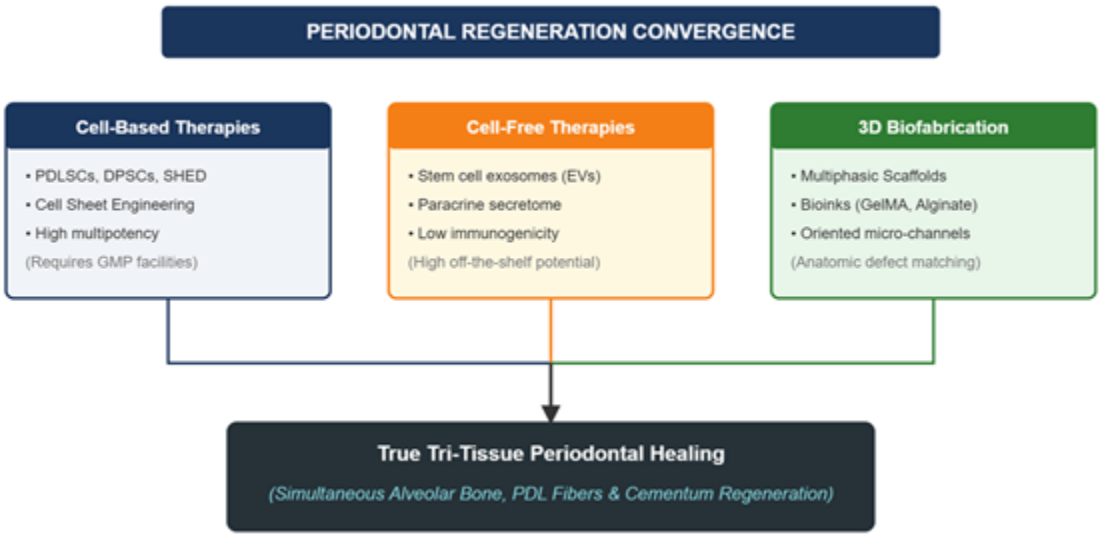

Figure 2. Diagram showing the convergence of cell-based, cell-free, and 3D biofabrication approaches.

Next-Generation Biofabrication: 3D Bioprinting and Smart Materials

The primary structural challenge in periodontal engineering lies in recreating the complex, multi-tissue interface composed of bone, oriented PDL fibers, and cementum (Bartold & Gronthos, 2016; Ivanovski et al., 2014). Single-phase scaffolds lack the capacity to direct distinct cell types simultaneously. Consequently, multiphasic and tri-layered scaffolds have been developed to match the structural requirements of each tissue layer (Vaquette et al., 2013; Sowmya et al., 2017).

In additive manufacturing and 3D bioprinting, patient-specific CBCT imaging is used to create patient-specific scaffold geometry (Raszewski et al., 2024; Pilipchuk et al., 2016). Technologies such as extrusion printing, SLA, and DLP allow for the deposition of bioinks—like GelMA, alginate, and hyaluronic acid hydrogels—containing cells or growth factors (Pilipchuk et al., 2016; Mansoori et al., 2024). Moreover, advanced 3D-printed scaffold designs contain aligned micro-channels allowing PDL fibroblasts to orient themselves perpendicular to the bone and cementum matrices to form natural Sharpey's fibers (Pilipchuk et al., 2016; Sowmya et al., 2017).

However, the clinical application of bioprinted scaffolds was introduced by Rasperini et al., (2015) who described a long-term clinical case report of a personalized 3D-printed biodegradable PCL scaffold. Despite the successful implementation of the technique, it gave us valuable information regarding the scaffold degradation rate: a slower rate led to wound dehiscence and exposure problems (Ivanovski et al., 2014; Rasperini et al., 2015). Today's trends include the use of "smart hydrogels" and 4D bioprinting—materials that can change shape or release agents in response to environmental changes (Chang et al., 2021; Giannobile & Ma, 2022).

Technological Protocols Comparison

To contextualize the evolution of regenerative approaches, Table 1 compares the clinical and biological parameters across four main technical paradigms.

Table 1. Comparison of Periodontal Regenerative Approaches across Technical Eras.

Feature / Paradigm	Mechanical Barrier Era (GTR) (Gottlow et al., 1986; Murphy et al., 2018; Needleman et al., 2006)	Biologically Driven (EMD / PRF) (Hammarström, 1997; Ghanaati et al., 2014; Miron et al., 2017)	Cell & Cell-Free Approaches (Seo et al., 2004; Iwata et al., 2009; Liu et al., 2022)	Next-Gen Biofabrication (3D) (Raszewski et al., 2024; Sowmya et al., 2017; Rasperini et al., 2015)
Primary Mechanism	Physical exclusion of epithelium	Chemical signaling and chemotaxis	Paracrine signaling & cell replacement	Spatial guidance & multi-tissue delivery
Defect Selectivity	High (Requires space maintenance)	Moderate to High	High (Applicable to complex loss)	Custom-fitted to any defect anatomy.
Surgical Invasiveness	Moderate to High	Low (Flapless / MIST compatibility)	Low to Moderate	Low (Minimal prep, precise fit)
Handling / Complexity	Technique sensitive (Membrane collapse)	Simple (Injectable / Gel form)	Complex handling & transport	Pre-fabricated patient-specific placement
Primary Limitations	Membrane exposure, lack of cell stimulation	Limited volume stability in large defects	GMP costs, ethical/regulatory barriers	Degradation rate matching, cost
Clinical Outcome	Variable bone fill, CAL gain	High predictability, minimal morbidity	Accelerated soft/hard tissue healing	Integrated bone-PDL-cementum repair

4. CONCLUSION

The advancement in periodontal regeneration has shifted from the mechanical elimination of cells using the guided tissue regeneration approach to biological interventions that include growth factors, enamel matrix proteins, and fibrin matrices to stimulate tissue repair. While bioactive materials like EMD and PRF are very efficient in ensuring wound healing and clinical effectiveness, one-stage biomaterials face certain limitations when it comes to multi-tissue injuries. Exosomes may serve as the optimal means of intervention in this case by providing the same paracrine signaling cues for regeneration but without the need to deal with regulatory and immunogenicity concerns associated with the use of stem cell therapy. Besides, multiphase scaffolding along with 3D printing technology makes it possible to produce scaffolds that will be anatomically accurate and provide for the guidance of the perpendicular alignment of PDL fibers alongside alveolar bone and cementum. It is essential to direct further research towards optimization of kinetics of bioink degradation, determination of appropriate dosage for cell-free interventions, and carrying out clinical trials to assess cost-effectiveness and efficacy of these approaches. The ultimate measures that should be taken to bring advanced bioprinting solutions and exosome interventions into clinical practice are regulation compliance, cost efficiency, and development of an appropriate GMP production process.

Acknowledgments

We thank all co-authors and institutional staff for their support during the preparation of this review.

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Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

Funding

This research did not receive any external funding like specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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