International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Regenerative Materials Used in Periodontology: Current Evidence, Clinical Applications, and Future Perspectives

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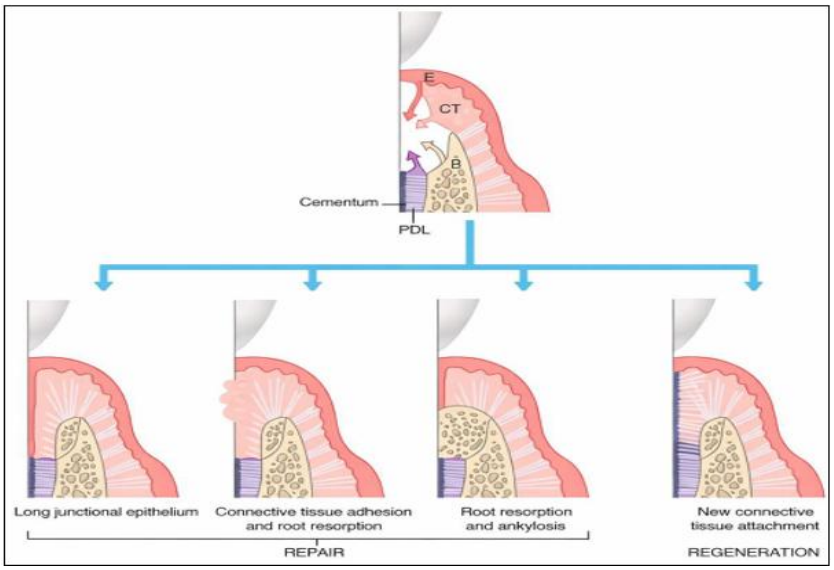
Abstract: ***Periodontal regeneration remains the ultimate goal in periodontitis therapy, as conventional treatment primarily arrests disease progression without restoring the lost periodontal attachment apparatus. True regeneration involves the coordinated formation of new cementum, periodontal ligament, and alveolar bone and depends on progenitor cells, signalling molecules, extracellular matrix components, and an appropriate healing environment. Advances in biomaterial science, molecular biology, and tissue engineering have transformed regenerative therapy from simple bone replacement to biologically driven approaches. Current regenerative materials include bone grafts, barrier membranes, biologic mediators, platelet concentrates, extracellular matrix derivatives, stem cell-based therapies, and advanced scaffolds. Autogenous bone remains the biological gold standard because of its osteogenic, osteoinductive, and osteoconductive properties, although donor-site morbidity has led to the use of allografts, xenografts, and synthetic substitutes. Guided tissue regeneration has evolved through improved membrane technology, while biologic agents such as enamel matrix derivative, platelet-derived growth factor, fibroblast growth factor-2, and bone morphogenetic proteins enhance regenerative potential. Emerging approaches include platelet-rich fibrin, injectable PRF, hyaluronic acid, mesenchymal stem cells, extracellular vesicles, nanotechnology, and three-dimensional bioprinting. No single material has demonstrated consistent superiority across all clinical situations. Current evidence increasingly favours combination approaches integrating scaffolds with biologically active molecules to optimise regeneration. This review critically evaluates regenerative materials used in periodontology, their biological mechanisms, clinical evidence, advantages, limitations, and emerging developments that will shape future periodontal regenerative therapy.***

Keywords: Periodontal regeneration, regenerative materials, bone grafts, guided tissue regeneration, enamel matrix derivative, platelet-rich fibrin, stem cells, tissue engineering.

1. Introduction

Periodontitis is a chronic inflammatory disease characterised by the progressive destruction of the tooth-supporting tissues, including the periodontal ligament (PDL), cementum, and alveolar bone. It affects a substantial proportion of the global population and remains one of the principal causes of tooth loss in adults.[1] Beyond its impact on oral health, periodontitis has been associated with several systemic disorders, including diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, and adverse pregnancy outcomes, emphasising the importance of preserving periodontal health through effective regenerative strategies.[2]

The primary objective of conventional periodontal therapy is the elimination of microbial biofilm and resolution of inflammation. Although procedures such as scaling and root planing, open flap debridement, and supportive periodontal therapy are highly successful in controlling disease progression, they generally result in repair rather than regeneration of the periodontal tissues.[3] Repair is characterised by the formation of a long junctional epithelium or connective tissue adaptation without complete restoration of the original attachment apparatus.[4] In contrast, true periodontal regeneration requires the formation of new cementum with functionally oriented periodontal ligament fibres inserted into newly formed alveolar bone, thereby restoring both the anatomy and function of the periodontium.[5]



The biological foundation of periodontal regeneration was established by Melcher's hypothesis, which proposed that the type of cells repopulating the root surface determines the outcome of periodontal wound healing.[6] This concept fundamentally changed regenerative periodontal therapy by emphasising the importance of selective cell repopulation and subsequently led to the development of guided tissue regeneration (GTR).[7] Since then, considerable progress has been made in understanding the molecular events governing wound healing, enabling the development of biomaterials that actively influence cellular behaviour rather than simply filling periodontal defects.

Bone grafts represented the earliest regenerative materials used in periodontal therapy and continue to play an important role in the treatment of intrabony defects and furcation lesions.[2] Initially, autogenous bone was considered the treatment of choice because it provides viable osteogenic cells and has osteoconductive and osteoinductive properties. Nevertheless, concerns regarding donor-site morbidity, limited graft availability, and increased surgical complexity stimulated the search for alternative biomaterials.[4] Consequently, allografts, xenografts, and synthetic alloplastic substitutes have become integral components of modern regenerative therapy.[8] Each material possesses unique biological characteristics that influence its regenerative potential, handling properties, and clinical indications.

The introduction of barrier membranes further transformed regenerative therapy by allowing selective repopulation of periodontal defects by cells originating from the periodontal ligament and alveolar bone.[3] Clinical studies have consistently demonstrated that GTR can improve clinical attachment gain and radiographic bone fill compared with conventional surgical therapy, particularly in well-contained intrabony defects. However, clinical outcomes remain dependent on defect morphology, wound stability, patient-related factors, and meticulous plaque control.[9]

A breakthrough in regenerative periodontology occurred with the introduction of biologically active molecules that directly regulate cellular proliferation, differentiation, angiogenesis, and extracellular matrix formation.[10] Enamel matrix derivative (EMD) was the first biologic agent to demonstrate consistent clinical evidence supporting true periodontal regeneration.[11] Subsequently, recombinant growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), and bone morphogenetic proteins (BMPs) have shown considerable promise by enhancing osteogenesis and periodontal ligament regeneration through targeted molecular signalling pathways.[12] The landmark review by Giannobile and Somerman highlighted the clinical benefits of EMD and emphasised the emerging role of growth factor-based regenerative therapies.[13]

Recent years have witnessed an expansion of regenerative approaches beyond conventional grafting procedures.[14] Platelet concentrates such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), advanced PRF (A-PRF), and injectable PRF (i-PRF) have gained widespread popularity because they provide an autologous source of growth factors within a fibrin scaffold that supports both soft- and hard-tissue healing.[15] Similarly, naturally occurring extracellular matrix components, including hyaluronic acid and collagen-based biomaterials, have attracted considerable attention because of their anti-inflammatory, angiogenic, and wound-modulating properties.[16]

Perhaps the most exciting developments have emerged from the fields of tissue engineering and regenerative medicine.[17] Mesenchymal stem cells, extracellular vesicles, exosomes, nanostructured biomaterials, injectable hydrogels, and three-dimensional bioprinting are being actively investigated to overcome the biological limitations of conventional regenerative therapy[18]. These advanced technologies aim not only to replace lost tissues but also to recreate the complex biological microenvironment necessary for functional periodontal regeneration. Contemporary reviews suggest that the future of regenerative periodontology lies in multifunctional biomaterials capable of simultaneously providing structural support, controlled release of biologically active molecules, immunomodulation, and recruitment of endogenous stem cells.[19]

Despite the rapid evolution of regenerative materials, predictable regeneration remains challenging because numerous variables, including defect configuration, patient-related risk factors, biomaterial characteristics, and surgical technique, influence treatment outcomes. Moreover, no single regenerative material has consistently demonstrated superiority in all clinical situations. Consequently, contemporary periodontal regeneration increasingly relies on combined approaches that integrate bone grafts, barrier membranes, biologic mediators, and tissue-engineering concepts to maximise clinical success.

Against this background, the present review critically examines the currently available regenerative materials used in periodontology, with particular emphasis on their biological rationale, mechanisms of action, clinical evidence, advantages, limitations, and future perspectives. By integrating recent reviews and landmark studies, this article aims to provide a comprehensive overview of contemporary regenerative strategies and their role in improving the predictability of periodontal therapy. [20]

Current Regenerative Materials in Periodontology: Biologic Mediators and Platelet Concentrates

The introduction of biologic mediators has significantly advanced periodontal regeneration by targeting the molecular mechanisms that govern wound healing rather than simply providing structural support. Unlike conventional graft materials, these agents regulate cell recruitment, proliferation, differentiation, angiogenesis, and extracellular matrix synthesis, thereby enhancing the regenerative potential of periodontal tissues. Their integration with bone grafts and barrier membranes has shifted periodontal therapy towards biologically driven regeneration.[12]

Enamel Matrix Derivative (EMD)

Enamel matrix derivative (EMD) was the first biologic agent to gain widespread clinical acceptance for periodontal regeneration. Derived from porcine enamel matrix proteins, predominantly amelogenins, EMD mimics the events of root development by promoting cementogenesis and periodontal ligament formation. Experimental studies have demonstrated

that EMD enhances proliferation and migration of periodontal ligament fibroblasts, stimulates osteoblast differentiation, increases collagen synthesis, and suppresses epithelial downgrowth, collectively creating a favourable environment for regeneration.[21]

Clinical evidence consistently supports the use of EMD in intrabony periodontal defects. Compared with open flap debridement alone, EMD significantly improves clinical attachment level gain, probing depth reduction, and radiographic bone fill. Histological studies further demonstrate the formation of new acellular cementum with functionally oriented periodontal ligament fibres, indicating true periodontal regeneration rather than repair. The systematic review by Giannobile and Somerman concluded that EMD provides predictable regenerative outcomes and remains one of the most extensively validated biologic mediators in periodontology. [22]

Despite these favourable outcomes, EMD is not universally effective. Regenerative success depends on defect morphology, surgical technique, and patient-related factors, while its relatively high cost may limit routine clinical application. Nevertheless, current evidence suggests that EMD performs particularly well in contained intrabony defects and can further enhance regenerative outcomes when combined with bone graft materials.[10]

Recombinant Growth Factors

Growth factors regulate virtually every stage of periodontal wound healing by controlling cellular migration, proliferation, differentiation, and angiogenesis. Advances in recombinant biotechnology have enabled the clinical application of several growth factors, among which platelet-derived growth factor (PDGF), bone morphogenetic proteins (BMPs), and fibroblast growth factor-2 (FGF-2) have demonstrated the greatest regenerative potential.[13]

Recombinant human PDGF-BB has shown encouraging results when combined with osteoconductive scaffolds such as β-tricalcium phosphate or allografts. By stimulating fibroblast proliferation, angiogenesis, collagen synthesis, and osteoblastic differentiation, PDGF enhances both soft tissue and hard tissue healing. Clinical trials have consistently reported greater clinical attachment gain and radiographic bone formation compared with conventional surgical therapy.[11]

Bone morphogenetic proteins, particularly BMP-2, possess potent osteoinductive properties capable of inducing mesenchymal stem-cell differentiation into osteoblasts. Although BMPs have demonstrated remarkable success in maxillofacial reconstruction and implant dentistry, their routine use in periodontal defects remains limited because of concerns regarding excessive bone formation, ankylosis, and cost.[12]

FGF-2 has emerged as another promising biologic mediator because of its ability to promote angiogenesis while simultaneously stimulating periodontal ligament regeneration. Recent randomised clinical trials have demonstrated significant improvements in clinical attachment gain and radiographic defect fill following topical application of recombinant FGF-2. Collectively, these findings indicate that growth factors represent valuable adjuncts rather than replacements for conventional regenerative materials, with their greatest benefit observed when incorporated into combination regenerative protocols.

Platelet Concentrates

Autologous platelet concentrates have become an integral component of regenerative periodontal therapy because they provide a natural source of growth factors within a fibrin matrix that supports wound healing. Unlike recombinant proteins, platelet concentrates deliver multiple biologically active molecules simultaneously, including PDGF, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and epidermal growth factor (EGF). These molecules collectively promote angiogenesis, collagen synthesis, cellular proliferation, and extracellular matrix remodelling.[25]

Platelet-rich plasma (PRP) represented the first generation of platelet concentrates but has gradually been replaced by platelet-rich fibrin (PRF) because PRF requires no anticoagulants or exogenous thrombin and forms a dense fibrin network capable of sustained growth factor release. Modifications such as advanced PRF (A-PRF) and injectable PRF (i-PRF) have further enhanced leukocyte content and prolonged cytokine release, thereby improving tissue healing and regenerative potential.[26]

Systematic reviews generally indicate that PRF significantly improves soft tissue healing and may enhance clinical attachment gain and radiographic bone fill when used as an adjunct to bone grafting procedures. However, PRF alone rarely achieves complete periodontal regeneration, and its greatest clinical benefit appears to be in combination with graft materials, barrier membranes, or biologic mediators. Variability in centrifugation protocols and preparation techniques remains an important limitation when interpreting the available literature.[16]

Overall, platelet concentrates are attractive because they are autologous, inexpensive, easy to prepare, and associated with minimal adverse effects. Nevertheless, further well-designed randomised clinical trials with standardised preparation protocols are required before definitive recommendations regarding superiority among different platelet concentrates can be established.

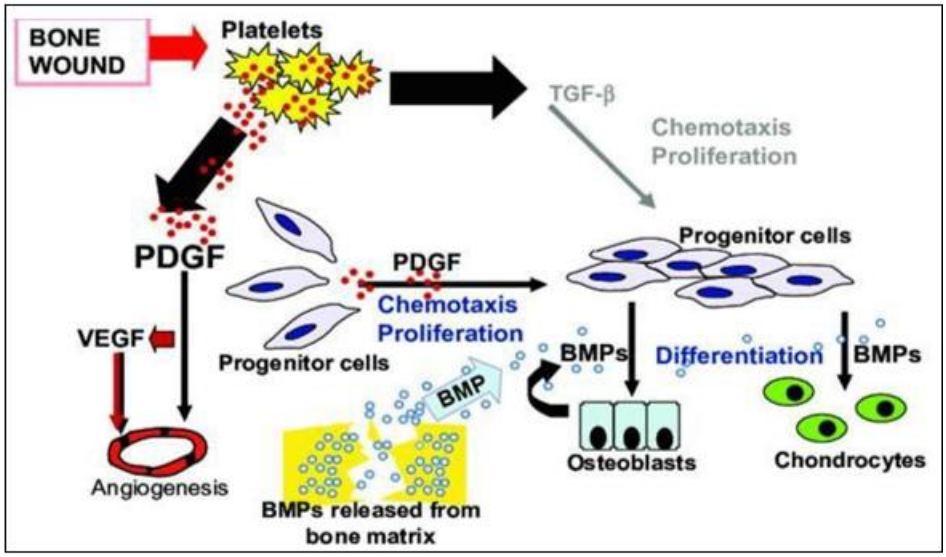
Emerging Regenerative Materials: Hyaluronic Acid, Stem Cells, Exosomes, and Smart Biomaterials

The limitations of conventional regenerative approaches have accelerated the development of biologically active materials capable of modulating the periodontal microenvironment rather than merely replacing lost tissues. Contemporary regenerative research increasingly focuses on biomaterials that simultaneously promote angiogenesis, regulate inflammation, recruit endogenous stem cells, and provide controlled delivery of bioactive molecules. Among these, hyaluronic acid, mesenchymal stem cells, extracellular vesicles, and nanotechnology-based biomaterials represent the most promising innovations in periodontal regeneration.

Hyaluronic Acid

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan that forms an essential component of the extracellular matrix. Beyond its structural role, HA regulates cell migration, proliferation, angiogenesis, and inflammatory responses, making it an attractive biomaterial for periodontal wound healing. Experimental studies have demonstrated that HA enhances fibroblast and osteoblast activity, promotes collagen synthesis, and accelerates angiogenesis while suppressing pro-inflammatory cytokines.

Clinical evidence suggests that adjunctive application of HA improves early soft tissue healing and may enhance clinical attachment gain in intrabony defects and gingival recession therapy. Nevertheless, improvements in hard tissue regeneration remain modest when HA is used alone. Consequently, current research has shifted toward combining HA with bone grafts, collagen membranes, or platelet concentrates to exploit potential synergistic effects. Such combination therapies appear to improve wound stability and create a biologically favourable environment for regeneration, although further long-term randomised clinical trials remain necessary before routine recommendations can be established.



Stem Cell-Based Therapy

Stem cell therapy represents one of the most promising developments in regenerative periodontology because it directly addresses the biological limitations of conventional regenerative materials. Mesenchymal stem cells (MSCs) derived from the periodontal ligament, bone marrow, dental pulp, gingiva, and adipose tissue possess the capacity for self-renewal and multilineage differentiation into osteoblasts, cementoblasts, and periodontal ligament fibroblasts.[17]

In addition to direct tissue formation, MSCs exert significant paracrine effects by secreting cytokines, chemokines, and growth factors that regulate inflammation, stimulate angiogenesis, and recruit endogenous progenitor cells. Preclinical studies consistently demonstrate enhanced bone formation, cementogenesis, and periodontal ligament regeneration following transplantation of MSC-based constructs. Early clinical investigations have also reported encouraging improvements in clinical attachment levels and radiographic bone fill. However, widespread clinical implementation remains constrained by challenges related to cell isolation, expansion, regulatory approval, manufacturing costs, and long-term safety. Consequently, stem cell therapy is currently regarded as an emerging rather than routine regenerative modality.

Exosomes and Extracellular Vesicles

Growing evidence indicates that many of the regenerative effects attributed to stem cells are mediated through extracellular vesicles, particularly exosomes. These nanosized vesicles contain proteins, lipids, messenger RNA, and microRNA capable of modifying the behaviour of recipient cells without requiring transplantation of living cells.

Exosomes have demonstrated the ability to stimulate osteogenic differentiation, enhance angiogenesis, regulate immune responses, and suppress excessive inflammation, thereby promoting a favourable regenerative microenvironment. Compared with stem-cell transplantation, exosome-based therapy offers several theoretical advantages, including lower immunogenicity, easier storage, reduced ethical concerns, and improved safety. Although current evidence is largely derived from laboratory and animal studies, extracellular vesicles are increasingly considered a promising cell-free alternative for future periodontal regeneration.[19]

Nanotechnology and Smart Biomaterials

Nanotechnology has transformed regenerative biomaterial design by enabling precise control over surface topography, porosity, drug delivery, and cellular interactions. Nanostructured hydroxyapatite, Electrospun nanofibers, injectable hydrogels, and bioactive nanoparticles have demonstrated improved osteoblast adhesion, vascularisation, and extracellular matrix deposition compared with conventional biomaterials.

Recent research has focused on multifunctional "smart" biomaterials capable of responding to changes in the local inflammatory environment through controlled release of antimicrobial agents, growth factors, or anti-inflammatory

molecules. Three-dimensional bioprinting further extends this concept by allowing fabrication of patient-specific scaffolds that closely replicate the anatomical architecture of periodontal tissues. Although these technologies remain largely experimental, they represent a major step toward personalised regenerative therapy and may substantially improve the predictability of periodontal regeneration in the future.

2. Clinical Perspective

The expanding range of regenerative materials has significantly improved treatment options for periodontal defects; however, the available evidence indicates that no single biomaterial consistently outperforms all others. Instead, successful regeneration depends upon careful case selection, defect morphology, meticulous surgical technique, wound stability, and effective plaque control. Biomaterial selection should therefore be individualised according to the clinical scenario rather than based solely on theoretical biological advantages.

Current evidence supports the use of combination regenerative strategies. Bone grafts provide structural support, barrier membranes facilitate selective cell repopulation, biologic mediators stimulate cellular activity, and platelet concentrates enhance wound healing. Emerging biomaterials such as hyaluronic acid, stem cells, and exosomes further complement these approaches by improving the biological environment necessary for tissue regeneration. Consequently, periodontal regeneration has evolved from isolated biomaterial application to integrated biologically driven treatment protocols.[23]

3. Future Perspectives

Future advances in periodontal regeneration are expected to focus on precision medicine and biomimetic tissue engineering. Rather than relying solely on passive scaffolds, next-generation regenerative materials are being designed to actively regulate cellular behaviour through controlled delivery of growth factors, antimicrobial agents, and immunomodulatory molecules. Gene therapy, extracellular vesicles, three-dimensional bioprinting, and artificial intelligence-assisted biomaterial design may further enhance treatment predictability by enabling patient-specific regenerative strategies.[26]

Nevertheless, translation of these technologies into routine clinical practice requires robust randomised clinical trials with standardised protocols, long-term follow-up, and cost-effectiveness analyses. Future research should also prioritise identification of biomarkers capable of predicting regenerative outcomes and guiding individualised treatment selection.[27]

4. Conclusion

Periodontal regeneration has evolved considerably from conventional bone grafting procedures to sophisticated biologically driven regenerative strategies. Current evidence demonstrates that autogenous bone, allografts, xenografts, alloplastic substitutes, guided tissue regeneration, enamel matrix derivative, recombinant growth factors, and platelet concentrates all contribute to improved clinical outcomes when applied appropriately. However, none of these materials consistently achieves complete and predictable regeneration in every clinical situation.[15]

Emerging technologies including hyaluronic acid, stem-cell therapy, extracellular vesicles, nanotechnology, and smart biomaterials have expanded the therapeutic possibilities by targeting the biological mechanisms underlying periodontal wound healing. Although these innovations show considerable promise, their routine clinical application remains limited by insufficient long-term evidence and regulatory challenges.[18]

Based on the currently available literature, the greatest regenerative success is achieved through combination therapies that integrate structural scaffolds with biologically active molecules while respecting fundamental surgical principles. Continued advances in tissue engineering and regenerative medicine are expected to shift periodontal therapy toward personalised, biomimetic approaches capable of achieving more predictable and functional regeneration of the periodontal attachment apparatus.

Table 1: Highlights the current and future regenerative materials in periodontal regeneration.
Classification of regenerative materials used in periodontology

Regenerative material	Mechanism of action	Clinical indications	Advantages	Limitations	Strength of current evidence
Autogenous bone	Osteogenesis, osteoinduction, osteoconduction	Deep intrabony defects, ridge augmentation	Gold standard, viable osteogenic cells	Donor-site morbidity, limited availability	High
Allografts (FDBA/DFDBA)	Osteoconduction ± osteoinduction	Intrabony defects, furcation defects	No second surgical site	Variable osteoinductive potential	High
Xenografts (DBBM)	Osteoconduction	Ridge preservation, peri-implant defects	Excellent volume stability	Slow resorption	High
Alloplasts (β-TCP, HA, BCP, Bioactive glass)	Osteoconduction	Small-to-moderate periodontal defects	Unlimited availability, no disease transmission	Limited biological activity	Moderate–High
Barrier membranes (Collagen, ePTFE)	Selective cell repopulation (GTR)	Intrabony and furcation defects	Improved attachment gain	Membrane exposure/premature degradation	High
Enamel Matrix Derivative (EMD)	Stimulates cementogenesis and PDL regeneration	Intrabony defects	Strong histologic evidence	Cost	High

Growth factors (PDGF, BMP-2, FGF-2)	Cellular signalling and differentiation	Advanced regenerative procedures	Enhanced bone formation	Cost and regulatory limitations	Moderate–High
Platelet concentrates (PRF, A-PRF, i-PRF)	Sustained release of autologous growth factors	Adjunct to regenerative surgery	Simple, autologous	Protocol variability	Moderate
Hyaluronic acid	Anti-inflammatory, angiogenic, extracellular matrix modulation	Soft tissue healing, intrabony defects	Excellent biocompatibility	Limited long-term evidence	Moderate
Stem cells & exosomes	Tissue engineering and paracrine signalling	Experimental regenerative therapy	Potential for true regeneration	Limited clinical evidence	Low–Moderate
Nanoscaffolds/3D bioprinting	Biomimetic scaffold with controlled drug delivery	Experimental	Personalized regeneration	Mostly preclinical	Low

Current reviews consistently show strong evidence for conventional regenerative materials (bone grafts, GTR, EMD), whereas cell-based and biomimetic therapies remain promising but require more clinical validation.

Landmark Clinical Evidence Supporting Periodontal Regeneration

Author	Year	Study design	Regenerative material	Principal finding
Melcher[6]	1976	Biological hypothesis	Cell repopulation	Established the biological basis of periodontal regeneration[6]
Nyman et al.[7]	1982	Clinical study	Guided Tissue Regeneration	Demonstrated selective cell repopulation [7]
Sculean et al.	Multiple studies	Clinical & histologic	EMD	Histologic evidence of new cementum and periodontal ligament formation [27]
Giannobile & Somerman[13]	2003	Systematic review	Growth factors & EMD	EMD showed the strongest clinical evidence among biologic mediators [12]
Cortellini & Tonetti[4]	Multiple RCTs	Randomised clinical trials	Regenerative surgery	Significant CAL gain in intrabony defects [30]
Miron et al.[15]	Recent systematic reviews	Meta-analysis	PRF	Improved soft tissue healing and clinical attachment gain [29]
Aslan & Rasperini	2025	Narrative review	Modern regenerative therapies	Combination therapies outperform isolated biomaterials [31]
Wang et al.	2025	Systematic review & meta-analysis	Regenerative surgery	Long-term CAL and PD improvements were maintained for ≥5 years, though superiority over open flap debridement was not consistently significant.[23]

Clinical Recommendations for Biomaterial Selection

Clinical scenario	Preferred regenerative strategy	Evidence-based rationale
Three-wall intrabony defect	EMD ± DFDBA/DBBM	Predictable CAL gain and defect fill
Two-wall intrabony defect	Bone graft + collagen membrane	Improved space maintenance
One-wall defect	Combination regenerative approach	Limited regenerative potential with single materials
Class II furcation	GTR + bone graft	Better attachment gain than debridement alone
Ridge preservation	DBBM + collagen membrane	Maintains ridge dimensions
Peri-implant defects	Xenograft + collagen membrane	Supports bone regeneration around implants
Patients with compromised healing	PRF/i-PRF adjunct	Enhanced early wound healing
Future personalised therapy	Stem cells/exosome-based scaffolds	Experimental; insufficient evidence for routine use

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