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Periodontology

RECENT ADVANCES IN PERIODONTAL REGENERATION: A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT Periodontal disease continues to be one of the most widespread oral health problems globally, and the regeneration of tissues lost to periodontitis has long been a central goal in periodontal therapy. Over the last four decades or so, our understanding of periodontal wound healing has grown considerably, and with it, the range of regenerative strategies available to clinicians. This review attempts to trace the journey of periodontal regeneration — from the early experiments, through the development of guided tissue regeneration (GTR), enamel matrix derivatives (EMD), growth factor-based therapies, platelet concentrates, and more recently, stem cell and tissue engineering approaches. The aim here is to provide a broad but thorough overview of the biological principles, clinical evidence, and emerging technologies in this rapidly evolving field. While remarkable progress has been made, it is worth noting that truly predictable and complete regeneration of the periodontal attachment apparatus remains, in many clinical scenarios, an ongoing challenge.

KEYWORDS : Periodontal Regeneration, Guided Tissue Regeneration, Enamel Matrix Derivative, Platelet-Rich Fibrin, Stem Cells, Tissue Engineering, Biomaterials, Growth Factors, Bone Grafts

INTRODUCTION

Periodontitis, as most of us learn early in our training, is a chronic inflammatory condition driven by microbial biofilms that progressively destroys the tooth-supporting structures — the gingiva, periodontal ligament (PDL), cementum, and alveolar bone [1]. It remains the leading cause of tooth loss in adults, and its systemic implications have only added urgency to the search for better treatments [2]. Conventional non-surgical and surgical therapies like scaling and root planing or open flap debridement (OFD) are effective at halting disease progression, but they generally result in tissue repair rather than true regeneration — that is, they produce a long junctional epithelium rather than the new cementum, new PDL fibers, and new alveolar bone that would constitute genuine regeneration [3,4].

This distinction between repair and regeneration, first clearly articulated by Melcher back in 1976 [5], has been the driving force behind decades of research. The ideal outcome — the formation of new cementum with inserting Sharpey's fibers, a functionally oriented PDL, and new supporting bone — remains the "holy grail" of periodontal therapy, so to speak.

What is exciting, however, is how far we have come. From the earliest barrier membrane experiments to today's work with stem cells, 3D-printed scaffolds, and exosome-based therapies, the field has evolved tremendously. This review is an attempt to bring together the key milestones and recent advances in periodontal regeneration, drawing from indexed literature spanning the early 1980s to 2025. The goal is not just to catalogue what has been done, but to try and make sense of where the field stands and where it might be heading.

Historical Foundations

Melcher's Hypothesis — Where It All Began

Any discussion of periodontal regeneration has to start with Melcher's seminal hypothesis. In 1976, Melcher proposed that after periodontal surgery, four different cell types compete to repopulate the root surface: gingival epithelial cells, gingival connective tissue cells, bone cells, and PDL cells [5]. His key insight was that only PDL-derived cells have the capacity to form a true new attachment — with cementum and functionally oriented fibers. This idea, simple as it sounds now, was really the intellectual foundation on which everything that followed was built [5,6].

The practical implication was obvious: if you could somehow keep the faster-growing epithelial and connective tissue cells out of the wound, and give the slower PDL cells a chance to do their thing, you might achieve genuine regeneration. That insight directly led to the concept of guided tissue regeneration.

The Pioneering Work of Nyman, Gottlow, and Karring

In the early 1980s, a group of Scandinavian researchers — Nyman, Karring, Lindhe, and a young graduate student named Gottlow — set out to test Melcher's hypothesis experimentally. Nyman et al. in 1982 published what is now considered one of the landmark papers in periodontology, demonstrating new attachment formation in humans using a simple cellulose acetate filter (a Millipore filter, actually found in Nyman's lab drawer, as the story goes) as a barrier to exclude epithelium from the healing wound [7]. Around the same time, their monkey studies confirmed that PDL cells indeed possessed this remarkable regenerative potential [8].

Gottlow et al. built on this in 1984 with their study showing new attachment as a result of what they termed "controlled tissue regeneration" [9], and further in 1986 with clinical case reports documenting the same in human patients [10]. These studies are really what gave birth to the concept of guided tissue regeneration as we know it today. Nyman later extended the biological principle to bone regeneration, coining the parallel concept of guided bone regeneration (GBR) [11].

It is hard to overstate the impact of this body of work. It fundamentally changed how we think about periodontal healing and opened the door to an entirely new era of regenerative periodontology.

Guided Tissue Regeneration

The Concept and First-Generation Membranes

The principle behind GTR is elegantly straightforward: place a physical barrier between the gingival flap and the root surface to mechanically prevent epithelial and connective tissue cells from migrating into the defect, thereby allowing the slower-migrating PDL cells, cementoblasts, and osteoblasts time to colonize the area and regenerate the lost tissues [7,12].

The first clinically used GTR membranes were non-resorbable, made from expanded polytetrafluoroethylene (ePTFE), developed commercially by W.L. Gore & Associates. These worked well enough, but there was an obvious drawback — they required a second surgery for removal, which increased patient discomfort and the risk of complications [12,13]. Still, Gottlow et al. showed in their 1992 follow-up study that the attachment gains achieved with GTR could be maintained for up to five years with good supportive care [14], which was encouraging.

The Shift to Resorbable Membranes

The need for a second surgery was a real limitation in clinical practice, and this drove the development of resorbable membranes made from collagen, polylactic acid (PLA), polyglycolic acid (PGA), and various copolymers. Collagen membranes, in particular — usually derived

from bovine or porcine sources — became the most widely adopted because of their good biocompatibility, hemostatic properties, and ease of handling [15,16]. Several comparative studies showed that resorbable membranes gave clinical results that were broadly similar to ePTFE, but with fewer complications, which was a clear win for patients [17,18].

What Do the Clinical Outcomes Actually Look Like?

The evidence base for GTR is now quite robust. Multiple Cochrane reviews and meta-analyses have confirmed that GTR produces statistically significant improvements in clinical attachment level (CAL) gain and probing depth (PD) reduction compared to OFD alone [19,20]. The catch, though, is that outcomes are very defect-dependent. Three-wall intrabony defects respond beautifully; two-wall defects are somewhat less predictable; and one-wall defects and Class III furcation involvements remain frustratingly difficult to treat [21]. Patient factors like smoking, diabetes, and oral hygiene compliance also play a major role, which any of us who have worked in the clinic can attest to.

Bone Grafting Materials

The Four Categories of Bone Grafts

Bone grafts have been a staple of regenerative periodontal surgery for decades, and they continue to be widely used. They essentially serve as scaffolds — filling the defect space and providing a framework for new bone to form on. The classic classification divides them into four groups [22,23]:

- **Autografts** remain the gold standard because they bring osteogenic cells, osteoinductive factors, and an osteoconductive matrix all in one package [24]. But the donor site morbidity and limited quantity available are real practical limitations.
- **Allografts —** particularly demineralized freeze-dried bone allograft (DFDBA) — have been popular because they can offer some osteoinductive potential through residual BMPs released during the demineralization process, without requiring a second surgical site [25,26].
- **Xenografts**, especially deproteinized bovine bone mineral (Bio-Oss®), are purely osteoconductive but have excellent biocompatibility and very slow resorption rates, which provides long-term space maintenance [27,28].
- **Alloplasts —** synthetics like hydroxyapatite, β-tricalcium phosphate (β-TCP), and bioactive glass — eliminate any risk of disease transmission and are available in unlimited quantities [29,30].

Clinical Evidence

Numerous RCTs have shown that bone grafting, alone or in combination with membranes, produces superior outcomes compared to OFD in terms of CAL gain, PD reduction, and defect fill [31,28]. The combination of bone grafts with GTR membranes seems to be especially beneficial in non-contained defects, where the graft provides the structural support that the membrane alone cannot [32,33].

Enamel Matrix Derivatives

The Biological Rationale

Enamel matrix derivative (EMD), commercially available as Emdogain® (Straumann), takes a fundamentally different approach from GTR. Rather than using a physical barrier, EMD attempts to recapitulate the biological events of tooth development. It is an extract of enamel matrix proteins from developing pig tooth germs, composed predominantly of amelogenins (over 90%), along with smaller amounts of ameloblastin, enamelin, and trace growth factors like TGF-β1 and BMP-2 [34,35]. The idea, first proposed by Hammarström in 1997, is that these proteins play a role in acellular cementum formation during development, and applying them to debrided root surfaces might trigger a similar regenerative cascade [34,36].

What the Evidence Shows

Quite a lot of research has gone into evaluating EMD, and the results have been generally positive. The Cochrane review by Esposito et al. in 2009, which pooled data from 13 RCTs, found that EMD produced statistically significant improvements in probing attachment level (about 1.1 mm on average) and probing depth reduction (about 0.9 mm) compared to controls at one year [37]. Interestingly, when EMD was compared head-to-head with GTR, there were no major differences in clinical outcomes, though the EMD-treated sites tended to have fewer postoperative complications [37,38]. A ten-year follow-up study by Sculean et al. confirmed that the clinical benefits of EMD treatment can be sustained long-term [39].

More recently, EMD has shown promise in minimally invasive surgical protocols for intrabony defects [40,41] and as an adjunct for gingival recession coverage when combined with coronally advanced flaps [42]. However, it is worth mentioning that for Class II furcation defects, the evidence for additional benefit from EMD is less convincing [42].

Growth Factors in Periodontal Regeneration

Platelet-Derived Growth Factor (PDGF)

Among the various growth factors studied for periodontal regeneration, PDGF — particularly the BB homodimer — has probably received the most clinical attention. It is a potent mitogen and chemoattractant for PDL cells, osteoblasts, and cementoblasts. Lynch et al. were among the first to demonstrate, back in 1989, that combining PDGF with IGF-1 could enhance periodontal regeneration in animal models [43]. This eventually led to the development of recombinant human PDGF-BB (rhPDGF-BB) combined with β-TCP, marketed as GEM 21S®, which received FDA approval for periodontal use.

The pivotal study was a large multicenter RCT by Nevins et al. in 2005, which demonstrated significant improvements in CAL gain and bone fill with rhPDGF-BB/β-TCP compared to β-TCP alone. Crucially, histological analysis confirmed true regeneration — new cementum, PDL, and bone [44]. That histological evidence is important, because clinical measurements alone cannot distinguish between regeneration and repair.

Bone Morphogenetic Proteins (BMPs)

BMPs, particularly BMP-2 and BMP-7, are powerful osteoinductive agents belonging to the TGF-β superfamily. Preclinical studies showed impressive alveolar bone regeneration with BMP-2 delivered via collagen sponges [45]. However, clinical translation in periodontology has been problematic. The doses required tend to be supra-physiological, and there have been concerns about unpredictable cementogenesis, ankylosis, and even root resorption at higher concentrations [46,47]. So while BMPs remain biologically fascinating, their routine clinical use in periodontal regeneration is still limited.

Fibroblast Growth Factor-2 (FGF-2)

FGF-2, or basic FGF, is worth highlighting because it represents one of the few growth factor products that has actually achieved regulatory approval for periodontal use. Kitamura et al. conducted a multi-center RCT in Japan showing that FGF-2 significantly promoted alveolar bone regeneration in intrabony defects [48]. A subsequent Phase III trial confirmed these results, and in 2016, FGF-2 (marketed as Regroth®) became the first growth factor-based periodontal product approved in Japan [49]. This was a significant milestone for the field.

Platelet Concentrates

From PRP to PRF — An Evolution

The idea of using the patient's own blood-derived growth factors for regeneration is inherently appealing. Platelet-rich plasma (PRP), introduced by Marx et al. in 1998, was the first attempt at harnessing this potential [50]. PRP concentrates platelets and their α-granule contents — PDGF, TGF-β, VEGF, IGF-1 — into a small volume for local application. While PRP showed some promise, its complex preparation protocol, the need for bovine thrombin, and the rather rapid and short-lived release of growth factors were significant limitations [51,52].

Platelet-rich fibrin (PRF), developed by Choukroun et al. in 2001, was a game-changer in many respects [53]. It is much simpler to prepare — just centrifuge a tube of blood without any anticoagulant — and the resulting fibrin matrix naturally traps platelets, leukocytes, and growth factors including TGF-β1, PDGF-AB, VEGF, and EGF. The beauty of PRF is that it provides a slow, sustained release of these factors over 7–14 days, which aligns much better with the biology of wound healing [54].

Clinical Applications of PRF

The clinical evidence for PRF in periodontal regeneration has grown substantially. Multiple RCTs have shown that adding PRF to OFD leads to significant improvements in PD reduction, CAL gain, and bone fill in intrabony defects. Systematic reviews by Miron et al. (2017) and Castro et al. (2021) both support the regenerative potential of PRF, either as a standalone adjunct or in combination with bone

grafts [55,56]. PRF has also been used successfully for gingival recession coverage and as a membrane substitute in GTR procedures.

Newer PRF Variants

The PRF story did not stop with the original Choukroun protocol. By tweaking centrifugation parameters, researchers have developed several variants with improved biological properties. Advanced PRF (A-PRF), introduced in 2014, uses lower centrifugal forces to capture more leukocytes and increase growth factor content. A-PRF+, developed subsequently, further reduces speed and time, and Fujioka-Kobayashi et al. (2017) showed it had significantly higher growth factor levels and better fibroblast stimulation than standard L-PRF [57]. There are also liquid formulations now — injectable PRF (I-PRF) and concentrated PRF (C-PRF) — that can be mixed with graft materials for easier clinical application [58]. The C-PRF protocol reportedly produces a threefold increase in growth factor release, which is quite impressive.

Stem Cell-based Therapies

The Promise of Mesenchymal Stem Cells

If there is one area that really captures the imagination in periodontal regeneration, it is stem cell therapy. Mesenchymal stem cells (MSCs), with their capacity for self-renewal and multilineage differentiation, theoretically offer the possibility of regenerating the entire periodontal attachment apparatus from scratch. Several MSC populations have been explored [59,60]:

- Periodontal ligament stem cells (PDLSCs) are perhaps the most promising. First isolated by Seo et al. in 2004, these cells can differentiate into cementoblasts, osteoblasts, and PDL fibroblasts, and when transplanted into animal models, they have generated cementum/PDL-like structures [61]. The fact that they come from the periodontal ligament itself makes them biologically very relevant.
- Bone marrow MSCs (BMSCs) were shown by Kawaguchi et al. (2004) to promote new bone, cementum, and PDL formation when seeded on scaffolds and placed in periodontal defects in dogs [62].
- Dental pulp stem cells (DPSCs), first characterized by Gronthos et al. in 2000, offer the advantage of being easily harvested from extracted teeth [63], while adipose-derived stem cells (ADSCs) are abundant and accessible from subcutaneous fat [64].

iPSCs and Clinical Trials

Induced pluripotent stem cells (iPSCs), based on Yamanaka's groundbreaking reprogramming work, offer the theoretical advantage of patient-specific pluripotent cells without the ethical issues of embryonic stem cells. However, concerns about tumorigenicity have slowed clinical translation [59].

On the clinical front, progress has been cautious but real. Iwata et al. (2018) reported results from a clinical trial using autologous PDL cell sheets for treating periodontal defects, demonstrating acceptable safety and preliminary efficacy [65]. But honestly, we are still in the early days here. Standardizing cell isolation, ensuring quality control, and demonstrating long-term safety and efficacy in large-scale trials remain major hurdles [59].

Tissue Engineering And Scaffold-based Approaches

The Triad: Cells, Scaffolds, and Signals

Modern tissue engineering for periodontal regeneration rests on the interplay of three components: cells that can form the desired tissues, scaffolds that provide a three-dimensional framework, and bioactive signals that direct cell behavior [66,67]. The challenge specific to the periodontium is its heterogeneity — you need to regenerate at least three distinct tissues (cementum, PDL, bone) in a precise spatial arrangement, which is no small feat.

Advances in Scaffold Design

Some of the most exciting work in recent years has been in scaffold technology. Multiphasic scaffolds — designs with distinct compartments mimicking the cementum, PDL, and bone layers — have been developed to address the multi-tissue challenge [66,68]. These bio-inspired constructs incorporate different compositions, pore architectures, and growth factor profiles in each layer.

Injectable hydrogels have also gained attention as versatile delivery vehicles. Their porous structure, biocompatibility, and tunable degradation make them well-suited for carrying stem cells and growth factors to defect sites [69]. Electrospun nanofiber scaffolds, which mimic the extracellular matrix at the nanoscale, have shown promise for PDL regeneration due to their favorable surface characteristics for cell attachment [70].

3D Bioprinting — The Frontier

Three-dimensional bioprinting is perhaps the most futuristic technology currently being explored for periodontal regeneration. It allows for precise, layer-by-layer deposition of cells, biomaterials, and growth factors, potentially creating patient-specific constructs guided by CBCT imaging data. Lee et al. (2014) and Park et al. (2017) demonstrated early proof-of-concept for multiphase bioprinted periodontal scaffolds [71,72]. We are still a long way from routine clinical application, but the potential is genuinely exciting.

Emerging Technologies

Gene Therapy

Gene therapy approaches aim to deliver sustained local expression of regenerative factors. Viral vectors encoding PDGF, BMP-2, and other factors have been tested in animal models with promising results [73,74]. Non-viral delivery systems are being explored to improve safety. However, clinical application remains distant due to regulatory and safety concerns.

Laser-Assisted Regeneration

Various laser modalities — Er:YAG, Nd:YAG, diode — have been investigated as adjuncts to regenerative surgery. Low-level laser therapy (photobiomodulation) may enhance wound healing and cell proliferation, but the clinical evidence is mixed, and there are no standardized protocols yet [75].

Exosomes and Extracellular Vesicles

This is a rapidly growing area. Small extracellular vesicles (exosomes) derived from dental stem cells carry bioactive proteins, mRNAs, and microRNAs that can modulate host cell behavior and promote regeneration — essentially offering the benefits of stem cells without actually transplanting cells [76]. It is still largely preclinical, but the concept of cell-free regenerative therapy is very attractive from a translational standpoint.

Nanoparticle Drug Delivery

Nanoparticle-based systems for delivering antimicrobial and regenerative agents to periodontal defects are being actively developed. These systems can provide sustained, localized release with minimal systemic effects [77,78]. While most work is still at the bench level, the potential for clinical impact is considerable.

Hyaluronic Acid

Hyaluronic acid (HA), a naturally occurring glycosaminoglycan, has gained interest as a regenerative adjunct due to its anti-inflammatory, pro-angiogenic, and wound healing properties. Recent clinical trials suggest favorable outcomes when HA is used alongside conventional regenerative materials in intrabony defects [79].

Minimally Invasive Surgical Techniques

It would be remiss not to mention the evolution of surgical technique, because the way we access and manage the defect has a huge impact on regenerative outcomes. Cortellini and Tonetti deserve enormous credit for developing the modified papilla preservation technique (1995), the simplified papilla preservation flap (1999), and the minimally invasive surgical technique (MIST) and modified MIST (M-MIST) in the late 2000s [80,81]. These approaches minimize flap reflection, preserve soft tissue architecture, and improve wound stability — all of which are critical for regeneration. Combined with microsurgical instruments and magnification, these techniques have consistently shown superior outcomes compared to traditional flap designs.

Combination Therapies

In clinical practice, many of us find that the best results come from combining different regenerative modalities rather than relying on any single approach. There is good evidence to support this. Combinations of bone grafts (e.g., DBBM) with EMD, or bone grafts with collagen membranes and PRF, tend to outperform single-modality treatments [39,82]. PRF combined with bone substitutes, for instance, can reduce the amount of graft material needed while improving vascularization of the grafted site [83]. The key is matching the regenerative strategy to the specific defect and clinical situation — there is no one-size-fits-all solution.

Current Challenges and Future Directions

Despite all the progress reviewed above, there are still significant

challenges that need to be addressed honestly:

1. Defect morphology remains the single biggest predictor of outcome. Horizontal bone loss, one-wall defects, and Class III furcations are still largely beyond our regenerative capabilities.
2. Patient-related factors — smoking, uncontrolled diabetes, poor compliance — continue to compromise outcomes in ways that even the best biomaterials cannot fully overcome.
3. Vascularization of large regenerated tissue volumes remains a fundamental biological challenge.
4. Creating truly biomimetic scaffolds that replicate the hierarchical organization of the periodontium is still more aspiration than reality.
5. Long-term stability of regenerated tissues under functional loading and the risk of disease recurrence need more investigation.
6. Regulatory, ethical, and cost barriers continue to slow the clinical translation of stem cell and gene therapies.
7. Lack of standardized protocols makes it difficult to compare studies and draw definitive conclusions.

Looking ahead, the most promising directions include smart biomaterials with spatiotemporally controlled release profiles, patient-specific 3D-bioprinted constructs, cell-free therapies using exosomes and conditioned media, immunomodulatory approaches that harness the host's own healing mechanisms, and perhaps even AI-guided treatment planning. The field is genuinely vibrant, and I believe we have reason to be cautiously optimistic about what the coming decades will bring.

CONCLUSION

Periodontal regeneration has come a remarkably long way since Melcher's hypothesis and the early membrane experiments of the 1980s. We now have an armamentarium that includes GTR, EMD, growth factors like rhPDGF-BB and FGF-2, platelet concentrates, stem cell therapies, and an ever-expanding array of biomaterials and scaffold technologies. The evidence clearly supports the use of these approaches for well-defined intrabony defects and select furcation involvements, and newer technologies like 3D bioprinting, exosome therapy, and nanoparticle-based delivery systems offer exciting possibilities for the future.

That said, we should be realistic. Complete, predictable regeneration of the entire periodontal attachment apparatus — especially in complex, multi-wall defects or advanced furcation involvements — remains elusive. Achieving this will require continued interdisciplinary collaboration between periodontists, materials scientists, cell biologists, and bioengineers. As students and clinicians, the most important thing we can do is stay critical, stay curious, and keep pushing the boundaries of what is possible.

REFERENCES

[1] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. 2005;366(9499):1809–1820.
[2] Caton JG, Armitage G, Berglundh T, et al. A new classification scheme for periodontal and peri-implant diseases and conditions. J Periodontol. 2018;89(Suppl 1):S1–S8.
[3] Han J, Menicanin D, Gronthos S, Bartold PM. Stem cells, tissue engineering and periodontal regeneration. Aust Dent J. 2014;59(Suppl 1):117–130.
[4] Cortellini P, Tonetti MS. Clinical concepts for regenerative therapy in intrabony defects. Periodontol 2000. 2015;68(1):282–307.
[5] Melcher AH. On the repair potential of periodontal tissues. J Periodontol. 1976;47(5):256–260.
[6] Melcher AH, McCulloch CA, Cheong T, Nemeth E, Shiga A. Cells from bone synthesize cementum-like and bone-like tissue in vitro and may migrate into periodontal ligament in vivo. J Periodontal Res. 1987;22(3):246–247.
[7] Nyman S, Lindhe J, Karring T, Rylander H. New attachment following surgical treatment of human periodontal disease. J Clin Periodontol. 1982;9(4):290–296.
[8] Nyman S, Gottlow J, Karring T, Lindhe J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. J Clin Periodontol. 1982;9(3):257–265.
[9] Gottlow J, Nyman S, Karring T, Lindhe J. New attachment formation as the result of controlled tissue regeneration. J Clin Periodontol. 1984;11(8):494–503.
[10] Gottlow J, Nyman S, Lindhe J, Karring T, Wennström J. New attachment formation in the human periodontium by guided tissue regeneration. Case reports. J Clin Periodontol. 1986;13(6):604–616.
[11] Nyman S. Bone regeneration using the principle of guided tissue regeneration. J Clin Periodontol. 1991;18(6):494–498.
[12] Gottlow J. Guided tissue regeneration using bioresorbable and non-resorbable devices: initial healing and long-term results. J Periodontol. 1993;64(11 Suppl):1157–1165.
[13] Murphy K. Postoperative healing complications associated with Gore-Tex periodontal material. Part II. Int J Periodontics Restorative Dent. 1995;15(6):548–561.
[14] Gottlow J, Nyman S, Karring T. Maintenance of new attachment gained through guided tissue regeneration. J Clin Periodontol. 1992;19(5):315–317.
[15] Christgau M, Schmalz G, Reich E, Wenzel A. Clinical and radiographical split-mouth-study on resorbable versus non-resorbable GTR-membranes. J Clin Periodontol. 1995;22(4):306–315.
[16] Eickholz P, Kim TS, Holle R. Regenerative periodontal surgery with non-resorbable and biodegradable barriers: results after 24 months. J Clin Periodontol. 1998;25(8): 666–676.
[17] Caffesse RG, Mota LF, Quinones CR, Morrison EC. Clinical comparison of resorbable and non-resorbable barriers for guided periodontal tissue regeneration. J Clin Periodontol. 1997;24(10):747–752.
[18] Cortellini P, Pini Prato G, Tonetti MS. The modified papilla preservation technique. J Periodontol. 1995;66(4):261–266.
[19] Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. Cochrane Database Syst Rev. 2006;(2):CD001724.
[20] Cortellini P, Tonetti MS. Clinical and radiographic outcomes of the modified minimally invasive surgical technique with and without regenerative materials. J Clin Periodontol. 2011;38(4):365–373.
[21] Laurell L, Gottlow J, Zybutz M, Persson R. Treatment of intrabony defects by different surgical procedures. A literature review. J Periodontol. 1998;69(3):303–313.
[22] Reynolds MA, Aichelmann-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. Ann Periodontol. 2003;8(1):227–265.
[23] Liang Y, Luan X, Liu X. Recent advances in periodontal regeneration: a biomaterial perspective. Bioact Mater. 2020;5(2):297–308.
[24] Camelo M, Nevins ML, Schenk RK, et al. Periodontal regeneration in human Class II furcations using purified rhPDGF-BB with bone allograft. Int J Periodontics Restorative Dent. 2000;20(6):564–577.
[25] Mellado JR, Salkin LM, Freedman AL, Stein MD. A comparative study of ePTFE periodontal membranes with and without DFDBA. J Periodontol. 1995;66(9):751–757.
[26] Bowers GM, Chadroff B, Carnevale R, et al. Histologic evaluation of new attachment apparatus formation in humans. Part III. J Periodontol. 1989;60(12):683–693.
[27] Camelo M, Nevins ML, Schenk RK, et al. Clinical, radiographic, and histologic evaluation of human periodontal defects treated with Bio-Oss and Bio-Gide. Int J Periodontics Restorative Dent. 1998;18(4):321–331.
[28] Sculean A, Stavropoulos A, Windisch P, et al. A randomized controlled clinical study of autogenous bone grafts versus enamel matrix derivative in intrabony defects. J Clin Periodontol. 2004;31:198–204.
[29] Kiliç AR, Öztürk A, Önem E. Comparison of bioactive glass and β-tricalcium phosphate as alloplastic grafting materials. J Dent Res. 1997;76:332.
[30] Froum SJ, Weinberg MA, Tarnow D. Comparison of bioactive glass synthetic bone graft particles and open debridement. J Periodontol. 1998;69(6):698–709.
[31] Lekovic V, Camargo PM, Weinlaender M, et al. A comparison between ePTFE membranes and combination therapies for regeneration of intrabony defects. Clin Oral Investig. 2000;4:111–119.
[32] Garrett S, Loos B, Chamberlain D, Egelberg J. Treatment of intraosseous periodontal defects with a combined adjunctive therapy. J Clin Periodontol. 1988;15(6):383–389.
[33] Iorio-Siciliano V, Andreuccetti G, Blasi A, et al. Clinical outcomes after treatment of non-contained intrabony defects. J Periodontol. 2014;85(11):1431–1439.
[34] Hammarström L. Enamel matrix, cementum development and regeneration. J Clin Periodontol. 1997;24(9 Pt 2):658–668.
[35] Gestrelius S, Andersson C, Johansson AC, et al. Formulation of enamel matrix derivative for surface coating. J Clin Periodontol. 1997;24(9 Pt 2):678–684.
[36] Heijl L, Heden G, Svärdström G, Östgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. J Clin Periodontol. 1997;24(9 Pt 2):705–714.
[37] Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects. Cochrane Database Syst Rev. 2009;(4):CD003875.
[38] Bosshardt DD. Biological mediators and periodontal regeneration: a review of enamel matrix proteins at the cellular and molecular levels. J Clin Periodontol. 2008;35(Suppl 8):87–105.
[39] Sculean A, Schwarz F, Milio A, et al. A retrospective study evaluating the ten-year clinical results after treatment of intrabony defects with enamel matrix proteins. J Clin Periodontol. 2008;35(8):79–85.
[40] Aimetti M, Ferrarotti F, Mariani GM, Romano F. A novel flapless approach versus minimally invasive surgery in periodontal regeneration with enamel matrix derivative proteins: a 24-month RCT. Clin Oral Investig. 2017;21:327–337.
[41] Aimetti M, Stasikelyte M, Mariani GM, et al. The flapless approach with and without enamel matrix derivatives for intrabony defects: a randomized controlled clinical trial. J Clin Periodontol. 2024;51:1112–1121.
[42] Bud E, Pop SI, Bud A, et al. Bony defect regeneration in periodontitis: a systematic review of the literature regarding the use of enamel matrix derivative proteins. Dent J. 2025;13:92.
[43] Lynch SE, Williams RC, Polson AM, et al. A combination of platelet-derived and insulin-like growth factors enhances periodontal regeneration. J Clin Periodontol. 1989;16(8):545–548.
[44] Nevins M, Giannobile WV, McGuire MK, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter RCT. J Periodontol. 2005;76(12):2205–2215.
[45] Wikesjö UME, Qahash M, Thomson RC, et al. rhBMP-2 significantly enhances guided bone regeneration. Clin Oral Implants Res. 2004;15(2):194–204.
[46] Giannobile WV. Periodontal tissue engineering by growth factors. Bone. 1996;19(1 Suppl):23S–37S.
[47] Ripamonti U, Reddi AH. Tissue engineering, morphogenesis, and regeneration of the periodontal tissues by bone morphogenetic proteins. Crit Rev Oral Biol Med. 1997;8(2):154–163.
[48] Kitamura M, Akamatsu M, Machigashira M, et al. FGF-2 stimulates periodontal regeneration: results of a multi-center randomized clinical trial. J Dent Res. 2008;87(10):921–927.
[49] Kitamura M, Akamatsu M, Kawanami M, et al. Randomized placebo-controlled and controlled non-inferiority Phase III trials comparing trafermin and enamel matrix derivative in periodontal regeneration. J Bone Miner Res. 2016;31(4):806–814.
[50] Marx RE, Carlson ER, Eichstaedt RM, et al. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(6):638–646.
[51] Creeper F, Ivanovski S. Effect of autologous and allogenic platelet-rich plasma on human gingival fibroblast function. Oral Dis. 2012;18(5):494–500.
[52] Dohan DM, Choukroun J, Diss A, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):e37–44.
[53] Choukroun J, Adda F, Schoeffer C, Vervelle A. PRF: an opportunity in perio-implantology (in French). Implantodontie. 2001;42:55–62.
[54] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158–167.
[55] Miron RJ, Zucchelli G, Pikos MA, et al. Use of platelet-rich fibrin in regenerative dentistry: a systematic review. Clin Oral Investig. 2017;21(6):1913–1927.
[56] Castro AB, Meschi N, Teles A, et al. Regenerative potential of leucocyte- and platelet-rich fibrin. Part A: intrabony defects, furcation defects and periodontal plastic surgery. J Clin Periodontol. 2021;48(1):77–95.
[57] Fujioka-Kobayashi M, Miron RJ, Hernandez M, et al. Optimized platelet-rich fibrin with the low-speed concept: growth factor release, biocompatibility, and cellular

response. J Periodontol. 2017;88(1):112–121.
[58] Miron RJ, Chai J, Zheng S, et al. A novel method for evaluating and quantifying cell types in platelet rich fibrin and an introduction to horizontal centrifugation. J Biomed Mater Res A. 2020;107(10):2257–2271.
[59] Bharuka T, Shukla P, Agrawal M, et al. Advancements in periodontal regeneration: a comprehensive review of stem cell therapy. Cureus. 2024;16(2):e54115.
[60] Huang TH, Chen JY, Suo WH, et al. Unlocking the future of periodontal regeneration: an interdisciplinary approach to tissue engineering and advanced therapeutics. Biomedicines. 2024;12(5):1090.
[61] Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet. 2004;364(9429):149–155.
[62] Kawaguchi H, Hirachi A, Hasegawa N, et al. Enhancement of periodontal tissue regeneration by transplantation of bone marrow mesenchymal stem cells. J Periodontol. 2004;75(9):1281–1287.
[63] Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci USA. 2000;97(25):13625–13630.
[64] Zhang X, Zhou Y, Xu M, et al. Adipose-derived stem cells for periodontal tissue regeneration. Stem Cell Res Ther. 2020;11:416.
[65] Iwata T, Yamato M, Washio K, et al. Periodontal regeneration with autologous periodontal ligament-derived cell sheets — a safety and efficacy study in ten patients. Regen Ther. 2018;9:38–44.
[66] Liang Y, Luan X, Liu X. Recent advances in periodontal regeneration: a biomaterial perspective. Bioact Mater. 2020;5(2):297–308.
[67] Ivanovski S, Vaquette C, Gronthos S, Hutmacher DW, Bartold PM. Multiphasic scaffolds for periodontal tissue engineering. J Dent Res. 2014;93(12):1212–1221.
[68] Ivanovski S, Vaquette C, Gronthos S, Hutmacher DW, Bartold PM. Multiphasic scaffolds for periodontal tissue engineering. J Dent Res. 2014;93(12):1212–1221.
[69] Pan Q, Zong Z, Li H, et al. Hydrogel design and applications for periodontitis therapy: a review. Int J Biol Macromol. 2025;284(Pt 1):137893.
[70] Bottino MC, Thomas V, Schmidt G, et al. Recent advances in the development of GTR/GBR membranes for periodontal regeneration — a materials perspective. Dent Mater. 2012;28(7):703–721.
[71] Lee CH, Hajibandeh J, Suzuki T, et al. Three-dimensional printed multiphase scaffolds for regeneration of periodontium complex. Tissue Eng Part A. 2014;20(7–8): 1342–1351.
[72] Park CH, Rios HF, Taut AD, et al. Image-based, fiber guiding scaffolds: a platform for regenerating tissue interfaces. Tissue Eng Part C Methods. 2014;20(7):533–542.
[73] Jin Q, Anusaksathien O, Webb SA, et al. Engineering of tooth-supporting structures by delivery of PDGF gene therapy vectors. Mol Ther. 2004;9(4):519–526.
[74] Giannobile WV, Lee CS, Tomala MP, et al. Platelet-derived growth factor gene delivery for application in periodontal tissue engineering. J Periodontol. 2001;72(6):815–823.
[75] Aoki A, Mizutani K, Schwarz F, et al. Periodontal and peri-implant wound healing following laser therapy. Periodontol 2000. 2015;68(1):217–269.
[76] Hua S, Bartold PM, Gulati K, et al. Periodontal and dental pulp cell-derived small extracellular vesicles: a review of the current status. Nanomaterials. 2021;11(7):1858.
[77] Wang D, Li Q, Xiao C, Wang H, Dong S. Nanoparticles in periodontitis therapy: a review of the current situation. Int J Nanomedicine. 2024;19:6857–6893.
[78] Gao S, Li H, Li Z, et al. Nanoparticle-based strategies for periodontal tissue regeneration. ACS Nano. 2025;19(7):7098–7116.
[79] Bertl K, Bruckmann C, et al. The effect of hyaluronic acid as an adjunct to periodontal therapy. Periodontol 2000. 2015;68:231–241.
[80] Cortellini P, Tonetti MS. A minimally invasive surgical technique with an enamel matrix derivative in the regenerative treatment of intrabony defects: a novel approach to limit morbidity. J Clin Periodontol. 2007;34(1):87–93.
[81] Cortellini P, Tonetti MS. Improved wound stability with a modified minimally invasive surgical technique in the regenerative treatment of isolated interdental intrabony defects. J Clin Periodontol. 2009;36(2):157–163.
[82] Sculean A, Schwarz F, Milio A, et al. A retrospective study evaluating the ten-year clinical results after treatment of intrabony defects with enamel matrix proteins and guided tissue regeneration. J Clin Periodontol. 2008;35(8):79–85.
[83] Simonpieri A, Del Corso M, Sammartino G, Dohan Ehrenfest DM. The relevance of Choukroun's platelet-rich fibrin and metronidazole during complex maxillary rehabilitations using bone allograft. Implant Dent. 2011;20(4):260–267.