Review Article

INTEGRATION OF REGENERATIVE TECHNIQUES IN THE TREATMENT OF PERIODONTAL CONDITIONS: META-ANALYSIS

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ABSTRACT

This meta-analysis evaluated the clinical efficacy of regenerative therapies for periodontal treatment, focusing on clinical attachment level gain and probing pocket depth reduction. A comprehensive literature search was conducted across Web of Science, Scopus, PubMed, Cochrane Library, and Google Scholar. Thirty-one studies published between 2019 and 2025 were included. Data analyses were performed using RevMan 5.4. The studies followed a PRISMA approach to ensure systematic reporting and consistency in methodology. The pooled results demonstrated that regenerative interventions significantly improved CAL gain (MD: 0.41 mm; 95% CI: 0.12-0.70; $I^2 = 78\%$), with platelet derivatives (MD: 0.45 mm; 95% CI: 0.04-0.86; $I^2 = 54\%$) and hydrogel-based therapies (MD: 0.53 mm; 95% CI: 0.03-1.04; $I^2 = 71\%$) showing the most consistent benefits. PPD reduction was modest (MD: 0.06 mm; 95% CI: -0.23-0.35; $I^2 = 84\%$), with platelet derivatives providing better outcomes (MD: 0.38 mm; 95% CI: -0.13-0.89; $I^2 = 67\%$). Growth factor interventions improved CAL (MD: 0.21 mm; 95% CI: -0.26-0.67; $I^2 = 48\%$) but showed variable PPD outcomes, while biomaterial-based scaffolds showed limited efficacy. Growth factor therapies improved CAL but produced variable PPD changes. Overall, findings support hydrogel- and platelet-based regeneration, highlighting the need for combined strategies, digital guidance, and extended follow-up for durable clinical outcomes.

Key words: Periodontal regeneration, Regenerative techniques, Guided tissue regeneration, Growth factors, Platelet concentrates, Bone grafts.

Introduction

Periodontal disease encompasses chronic inflammation of the gingiva, periodontal ligament, and alveolar bone, with gingivitis and periodontitis being the most common forms [1]. It is a major cause of tooth loss worldwide and affects about 46% of the U.S. population, with 10-15% presenting aggressive forms [2]. Conventional treatments such as scaling, root planning, and flap surgery primarily control infection and reduce inflammation but fail to regenerate lost alveolar bone, cementum, and periodontal ligament [3].

Bone grafting is vital in regeneration, using autografts, allografts, xenografts, or alloplasts. Bioactive scaffolds and growth factors enhance outcomes, though variability, technique differences, and high costs limit consistent success and accessibility [4].

Biologics, including recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and fibroblast growth factor-2 (rhFGF-2), have shown significant clinical benefits in regenerating bone, cementum, and ligament in intrabony and furcation defects [5]. Similarly, enamel matrix derivatives (EMD), particularly when combined with bone mineral substitutes, improve attachment gain and probing depth reduction [6]. Guided tissue regeneration (GTR) continues to yield long-term benefits, though further material optimization is needed [7].

Autografts remain the gold standard due to their osteogenic, osteoinductive, and osteoconductive capacities, but donor site morbidity and limited supply encourage the use of allografts, xenografts, and synthetics [8]. Stem cell–based therapies using mesenchymal stem cells from bone marrow, adipose, or dental tissues also show promising differentiation and regenerative outcomes [9].

Research gap

Despite progress in grafts, biologics, and stem cell–based materials, clinical outcomes remain inconsistent. Most studies are preclinical or short-term, and integration of immune modulation, cost-effectiveness, and minimally invasive approaches into practice remains limited.

Research novelty

This review synthesizes global evidence on regenerative periodontal therapies, focusing on biological mechanisms, innovative biomaterials, and minimally invasive surgery to enhance predictability, durability, and accessibility.

Objectives

This systematic review and meta-analysis evaluate the effectiveness of regenerative techniques, particularly growth factors, platelet concentrates, hydrogels, and biodegradable scaffolds, in improving clinical and radiographic outcomes.

Research question

1. To what extent do regenerative interventions improve clinical attachment level (CAL) gain in patients with periodontal disease?
2. How effective are these regenerative techniques in achieving probing pocket depth (PPD) reduction compared to conventional treatment approaches?
3. Do emerging biomaterials such as hydrogels and biodegradable scaffolds demonstrate superior or adjunctive benefits over established regenerative methods in periodontal regeneration?

Literature review

Biological and biomaterial innovations

Innovative biomaterials are expanding regenerative strategies. Sustained-release biomaterials enhance antibacterial and osteogenic effects [10]. 3D-printed membranes and scaffolds enable patient-specific GTR/GBR applications, though current evidence remains largely preclinical [11].

Molecular and immune-centric perspectives

Regulating the immune microenvironment is pivotal for predictable periodontal regeneration. Despite advances in scaffolds, stem cells, and 3D-printed tissues, translation is limited by uncontrolled inflammation [12]. Effective regeneration also requires precise immune modulation to support periodontal ligament stem cell function [13].

Emerging biological agents

Emerging molecular agents are gaining attention in periodontal regeneration. Hyaluronic acid combined with growth factors enhances outcomes, though robust validation is limited [14]. Mesenchymal stem cell-derived exosomes show promise due to biocompatibility and efficient delivery, but regulatory and mechanistic challenges remain [15].

Critical appraisal and global synthesis

Overall, these studies depict a promising yet fragmented global scenario in periodontal regeneration. While biologics like PRF and MSCs are effective, clinical use is limited by variability and scarce trials. Minimally invasive surgery shows comparable long-term results. Emerging biomaterials, 3D printing, exosomes, and HA offer potential, but immune regulation remains key.

Materials and Methods

Study design

A meta-analysis, following PRISMA guidelines, assessed the integration of regenerative techniques in periodontal treatment, focusing on their clinical outcomes.

Search strategy

A comprehensive literature search was conducted across Web of Science, Scopus, PubMed, Cochrane Library, and Google Scholar using Boolean search and MeSH terms. *("Periodontal conditions" OR "periodontitis" OR "periodontal defects") AND ("Regenerative techniques" OR "guided tissue regeneration" OR "bone graft" OR "platelet concentrates" OR "growth factors") AND ("Clinical outcomes" OR "tissue regeneration" OR "bone regeneration")*. **Figure 1** outlines the search strategy used to identify studies. From 24,205 records identified, 227 duplicates were removed, leaving 663 for screening. After exclusions and eligibility assessment, 31 studies remained, providing key evidence on clinical outcomes and efficacy of regenerative periodontal techniques [16–46].

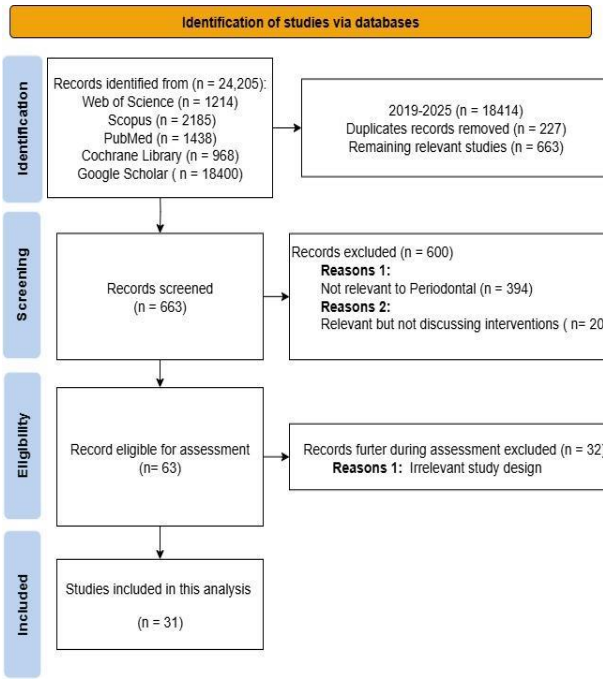

Figure 1. PRISMA flow diagram

Inclusion and exclusion criteria

Eligible studies (2019-2025) focused on periodontal regeneration in humans, reporting CAL gain and PPD reduction, with adequate follow-up. Non-human, review, or non-English studies were excluded.

Data extraction

Two independent reviewers extracted data. Discrepancies were resolved by consensus. Cohen's kappa was 0.89, indicating very strong agreement.

Statistical analysis

A random-effects model (RevMan 5.4) calculated pooled mean differences with 95% CI. Heterogeneity (I^2) and subgroup analyses (hydrogels, growth factors, platelet derivatives, scaffolds, autogenous techniques) were performed. Forest plots summarized the results.

Risk of bias assessment

Figures 2 and 3 summarize study bias using Cochrane RoB 2. Green = low, yellow = some concerns, red = high, visually depicting methodological quality across studies.

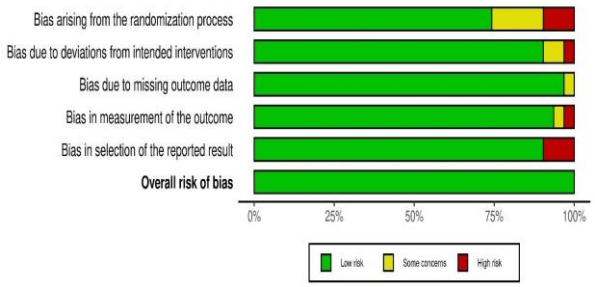

Figure 2. Risk of Bias Assessment Summary Plot

Figure 3. Traffic-Light Plot of Risk of Bias Assessment for Individual Study

Table 1. Characteristics of Included Studies

Author's / Year	Country	N	Follow-up Duration (Months)
Vela *et al.* 2024	Romania	60	≤ 6
Cetiner *et al.* 2024	Turkey	48	6
Akhter, 2025	Saudi Arabia	30	≤ 6
Abd El-Azeem *et al.* 2023	Egypt	45	6
Salama *et al.* 2025	Egypt	30	> 6
Adam *et al.* 2022	Germany	40	12
Seshima *et al.* 2022	Japan	32	4 8
Mubarak *et al.* 2023	Egypt	30	6
Sherif *et al.* 2025	Egypt	45	≤ 6
Panda *et al.* 2020	India	44	6
Górski *et al.* 2025	Poland	30	≤ 6
Aoki *et al.* 2021	Japan	38	2 4
Abdulrahman *et al.* 2022	Egypt	22	9
Goenka *et al.* 2025	India	40	≤ 6
Saito *et al.* 2019	Japan	44	6
Górski *et al.* 2019	Poland	30	4 8s
Razi *et al.* 2025	India	30	≤ 6
Ojha *et al.* 2024	India	11	12
Rodríguez-A *et al.* 2025	Spain	53	> 6
Venkatesan *et al.* 2021	India	50	6
Psg *et al.* 2025	India	64	> 6
Rout *et al.* 2024	India	30	6
Eshwar *et al.* 2023	India	40	9
Moreno *et al.* 2021	Spain	24	12
Ghallab *et al.* 2019	Egypt	20	6
Xu *et al.* 2019	China	54	12
Dolińska *et al.* 2025	Poland	41	≤ 6
Shoukheba *et al.* 2021	Egypt	20	12
Csifó-Nagy *et al.* 2021	Hungary	30	6
Gowdar *et al.* 2025	Saudi Arabia	40	≤ 6
Cagri Isler *et al.* 2022	Turkey	51	>6

Results and Discussion

Table 1 summarizes 31 studies across 10 countries, with 11-64 participants and 6 months to 4 years follow-up, assessing short- and long-term regenerative outcomes.

Table 2 summarizes regenerative interventions: growth factors, scaffolds, platelet derivatives, hydrogels, and autogenous techniques, showing improvements in CAL [47-52]. PPD, bone fill, defect resolution, and cost-effective outcomes across studies.

Table 2. Summary of Interventions and Key Findings

Author's / Year	Type of Technique Intervention	Key Findings
Growth Factors		
Seshima *et al*. 2022	rhFGF-2 + DBBM	Improved RBF; no CAL difference.
Aoki *et al*. 2021	rhFGF-2 + DBBM	Better RBF; similar CAL over 2 years.
Saito *et al*. 2019	rhFGF-2 + DBBM	CAL and PPD improved; best RBF with combo.
Moreno *et al*. 2021	NIPSA + EMD	Enhanced CAL, PPD, papilla fill.
Psg *et al*. 2025	SPPF + adjunctive LLLT vs SPPF alone	Greater CAL/PPD reduction, faster healing.
Shoukheba *et al*. 2021	Concentrated Growth Factor (CGF) + Bio-Oss	Higher bone density vs collagen membrane.
Cetiner *et al*. 2024	Antimicrobial photodynamic therapy (aPDT)	Adjunctive infection control and regeneration.
Scaffolds / Biomaterials		
Adam *et al*. 2022	GTPT	Improved CAL and PPD vs conventional
Goenka *et al*. 2025	Hydroxyapatite-coated titanium mesh vs uncoated	Higher CAL, PPD, and bone fill
Rout *et al*. 2024	MICBG	Both improved; ABG better in defect depth
Dolińska *et al*. 2025	DBBM + GTR ± antibiotics	Greater CAL gain; PD in both; recession only in control
Venkatesan *et al*. 2021	Amniotic membrane + BiCP	Slightly better CAL and defect healing
Górski *et al*. 2019	MPM	Stable CAL and bone density 4 yrs; no significant difference.
Ghallab *et al*. 2019	PPG	Improved outcomes; no significant difference
Platelet Derivatives		
Akhter, 2025	PRF + bone graft vs graft alone	Higher CAL gain, PPD reduction, and bone fill (68% vs 45%)
Salama *et al*. 2025	Sticky bone (xenograft + I-PRF) + repeated I-PRF vs xenograft	Greater CAL gain, PPD, IBD; defect fill 55.7% vs 45.1%
Mubarak *et al*. 2023	L-PRF + collagen membrane	Better defect base fill, no CAL gain difference
Sherif *et al*. 2025	PMPR + I-PRF ± Vitamin C	All improved; I-PRF/VitC reduced pain, slight bone gain
Panda *et al*. 2020	PRGF + SRP	Improved PPD reduction and CAL gain in deep pockets
Abdulrahman *et al*. 2022	Low-speed PRF + OFD	Improved CAL and PPD; no difference in bone fill or RLDD
Gowdar *et al*. 2025	PRF + OFD vs OFD	Higher CAL gain, PPD reduction, and bone fill
Xu *et al*. 2019	CGF + Bio-Oss vs. CGF alone	Improved CAL and PPD
Cagri Isler *et al*. 2022	Concentrated Growth Factor (CGF)	CM showed greater PPD reduction than CGF
Csifó-Nagy *et al*. 2021	Advanced PRF (A-PRF+)	As effective as EMD in CAL and PPD
Hydrogels		
Abd El-Azeem *et al*. 2023	RGD peptide-loaded hydrogel (MIST)	Improved CAL, PPD, and BMP-2 levels
Eshwar *et al*. 2023	Fucoidan-Chitosan hydrogel	Improved CAL and PPD
Rodríguez-A *et al*. 2025	Crosslinked HA (Hyadent BG®) + MIST/M-MIST vs EMD + MIST/M-MIST	Both improved CAL and PPD
Vela *et al*. 2024	Hyaluronic Acid (xHyA)	Improved CAL and PPD
Ojha *et al*. 2024	CPC-PLGA composite bone graft	Better bone fill and defect depth

Autogenous Techniques		
Górski *et al*. 2025	Autogenous cortical bone graft + GTR vs GTR	Greater CAL gain, PPD reduction; 70% vs 55% defect fill
Razi *et al*. 2025	Autogenous cortical bone graft + GTR vs GTR	Greater CAL gain, PPD reduction; 70% vs 55% defect fill

Figure 4 presents a meta-analysis of CAL gain from 25 studies on regenerative periodontal techniques. The pooled effect showed a mean difference of 0.41 mm with high heterogeneity (I^2 = 78%). Subgroup analyses revealed modest CAL improvements across growth factors, scaffolds, platelet derivatives, hydrogels, and autogenous techniques, with sensitivity analyses identifying several outliers that significantly reduced heterogeneity in most subgroups.

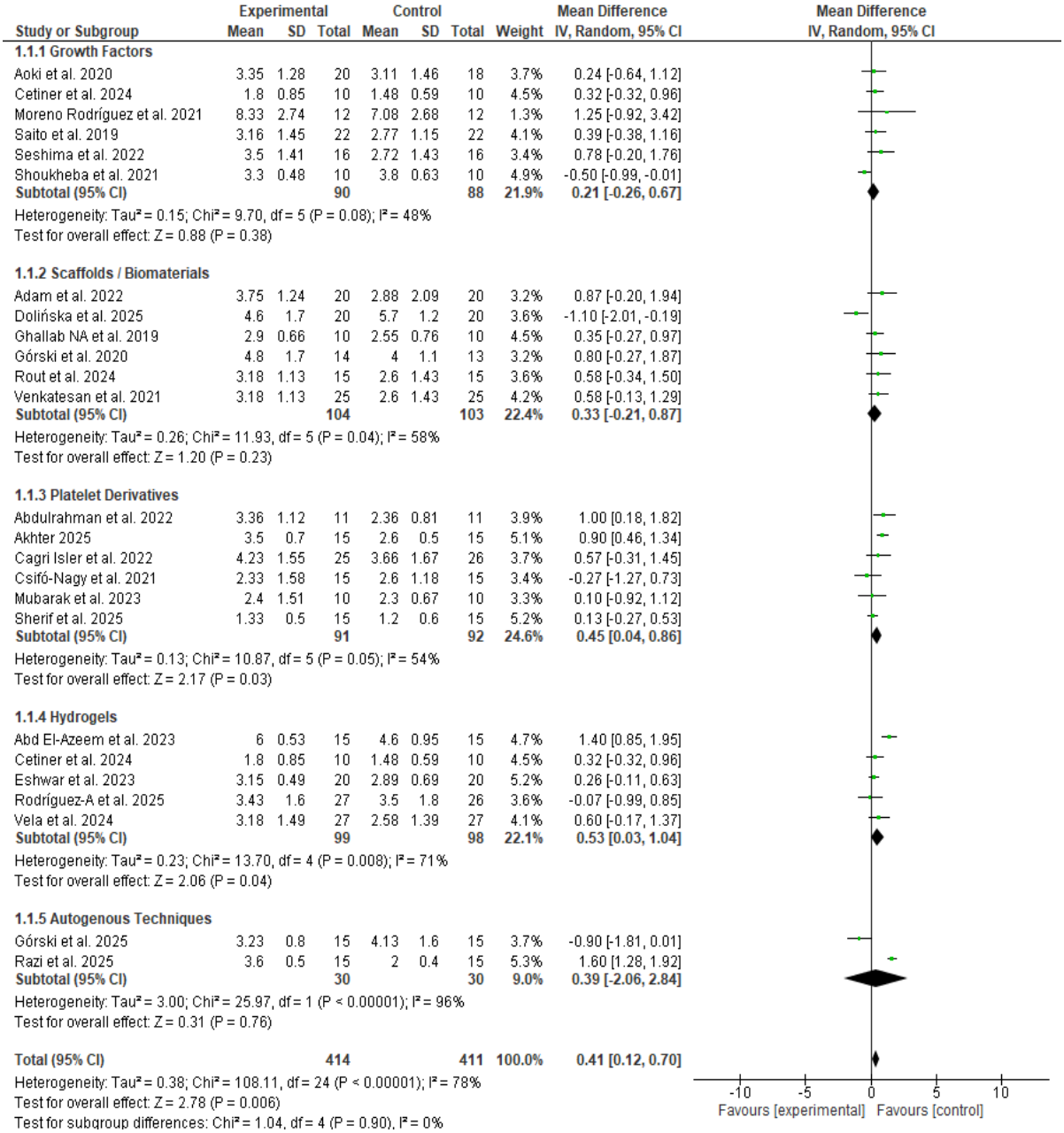

Figure 4. Forest Plot of Meta-Analysis for Clinical Attachment Level (CAL) Gain Across Different Regenerative Techniques in Periodontal Treatment

Figure 5 summarizes the meta-analysis of PPD reduction from 2 2 studies on regenerative techniques. The pooled mean difference was 0.06 mm (95% CI: -0.23–0.35) with high heterogeneity (I^2 = 84%). Subgroup analyses showed minimal or inconsistent reductions, with platelet derivatives showing the largest effect (0.38 mm).

Sensitivity analyses reduced heterogeneity in most subgroups, though autogenous techniques remained highly variable ($I^2 = 97\%$).

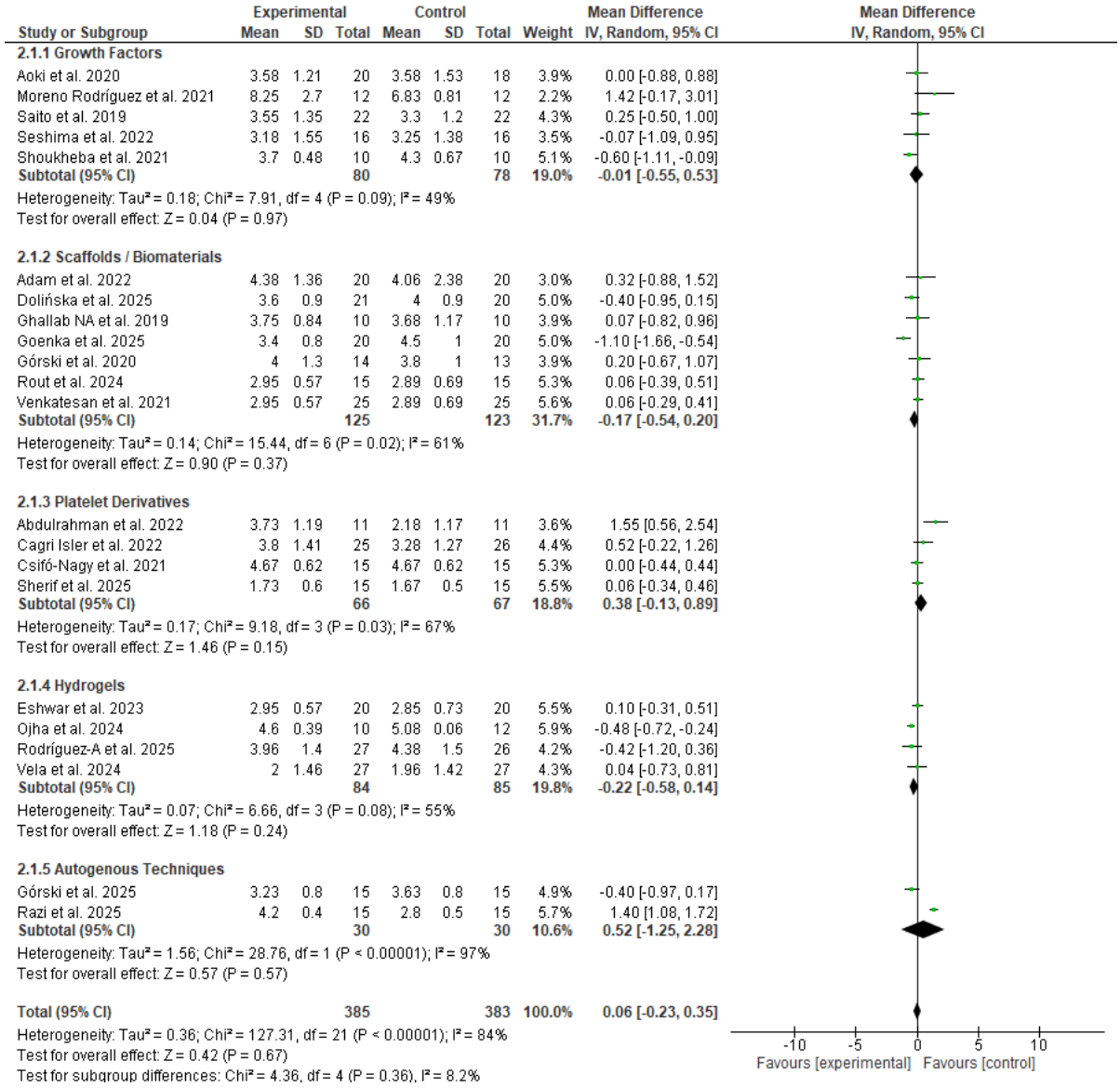

Figure 5. Forest Plot of Meta-Analysis for Probing Pocket Depth (PPD) Reduction Across Various Regenerative Techniques in Periodontal Treatment

Periodontal disease, a global health burden marked by progressive tissue destruction, poses challenges for predictable regeneration. This meta-analysis assessed regenerative techniques improving CAL, PPD, and bone fill across regions. Studies showed diverse methods of GTR were most effective for PPD reduction, and EMD + bone grafts yielded the highest CAL gains [53].

This study underscores the efficacy of hydrogel-based therapies, particularly RGD peptide-loaded, Fucoidan-Chitosan, and cross-linked hyaluronic acid in enhancing CAL gain, PPD reduction, and tissue healing with cost-effectiveness and fewer complications. However, PPD improvements varied by defect type and adjunctive therapy. aPDT and LED photobiomodulation offered additional regenerative benefits [54].

Growth factors such as rhFGF-2 with DBBM improved CAL and PPD in certain studies, especially in combination therapies. However, findings were inconsistent, with some trials showing no significant advantage over controls. CGF with Bio-Oss proved to be a cost-effective adjunct, highlighting the importance of patient-specific protocols [55].

The current analysis demonstrates that platelet derivatives PRF, PRGF, A-PRF+, CGF, and L-PRF consistently improve CAL, PPD, and bone fill in deep periodontal pockets. PRF combined with bone grafts achieved superior bone regeneration versus grafts alone. While outcomes vary

by defect type and adjunctive use, findings affirm platelet derivatives as effective regenerative adjuncts [56].

The current study suggests that Biomaterial-modified grafts and membranes, including CPC-PLGA composites, hydroxyapatite-coated titanium mesh, MICBG, and amniotic BiCP, improved bone fill, defect healing, and CAL gain versus conventional grafts. However, benefits were sometimes modest, indicating modifications alone may not ensure superiority. Recent evidence underscores that advanced scaffold designs, especially multiphasic and biomimetic architectures, enhance osteogenesis and defect resolution [57].

The current study indicates that Novel regenerative approaches improved CAL/PPD; autogenous grafts + GTR outperformed GTR alone, and PPG matched bioresorbables. However, high heterogeneity limits generalizability. A systematic review supports the use of PPG alongside open flap debridement for chronic periodontitis [58].

The current meta-analysis revealed a pooled CAL gain of 0.41 mm, with the highest values observed with hydrogels and the lowest with growth factors, indicating high heterogeneity that highlights the need for standardized protocols. Similarly, a study on orthodontic tooth movement in periodontitis-treated patients showed a CAL gain of 2.29 mm with high heterogeneity. These findings underline the need for further refinement in the methods used [59].

Meta-analysis revealed minimal overall PPD reduction. Platelet derivatives showed the greatest improvement, while hydrogels and growth factors varied. High heterogeneity suggests inconsistent outcomes; refinement of regenerative protocols is needed. A related study reported a 1.20 mm reduction, influenced by tooth type and jaw mobility [60].

This meta-analysis aligns with recent evidence, confirming that hydrogel-based scaffolds (Fucoidan-Chitosan, RGD peptides) and rhFGF-2 + DBBM enhance CAL and bone fill [61]. Surface modifications, particularly sandblasting combined with acid etching, enhance osseointegration by creating micro-rough surfaces that improve bone-to-implant contact and early tissue healing, ensuring better implant stability and longevity [62]. Similarly, photoactivation of implant surfaces provides higher ISQ values and greater long-term stability than conventional acid modification, supporting fixed dentures without increasing tissue complications [63]. Despite overall efficacy, heterogeneity highlights the need for standardized protocols, careful patient selection, and further research to optimize regenerative outcomes across populations.

Study limitations

The study showed high heterogeneity and small sample sizes, particularly in platelet-rich subgroups, limiting comparability and generalizability. Short follow-ups further restricted long-term assessment, underscoring the need for larger, standardized, and extended studies to improve evidence reliability and clinical relevance.

Conclusion

This meta-analysis of 31 clinical studies demonstrates that regenerative interventions provide modest yet significant CAL gains, with platelet derivatives and hydrogels showing the most consistent benefits. PPD reduction was less pronounced and marked by heterogeneity, particularly in autogenous techniques. Platelet concentrates, especially when combined with grafts, enhanced bone fill and healing, while hydrogels, such as cross-linked hyaluronic acid, offered cost-effective alternatives. Growth factors and scaffolds remain promising but variable, supporting their role as adjuncts. Future research should emphasize combined regenerative strategies, digital-assisted techniques, and long-term multicenter trials with standardized outcomes to ensure reproducibility, cost-effectiveness, and sustained periodontal health.

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Conflict of interest: None

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Ethics statement: This meta-analysis is based on secondary data derived from studies that have already been published. No new ethical approval was required for this analysis. However, all the primary studies included in this meta-analysis complied with ethical standards, as demonstrated by Institutional Review Board (IRB) approvals and informed consent obtained from the participants involved. The original studies ensured the protection of participants' rights and confidentiality, in line with ethical guidelines. All procedures were conducted in accordance with the Declaration of Helsinki and other relevant ethical principles, ensuring that participant welfare was prioritized throughout the research process.

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