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EFFECTS OF GLP-1 RECEPTOR AGONISTS ON PERIODONTAL HEALTH, ORAL WOUND HEALING, AND PERIODONTAL REGENERATION: A SYSTEMATIC REVIEW OF PRECLINICAL EVIDENCE

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Abstract

Background: *Periodontitis is a chronic inflammatory disease characterized by progressive destruction of the tooth-supporting tissues and is strongly associated with metabolic disorders such as type 2 diabetes mellitus. Glucagon-like peptide-1 receptor agonists (GLP-1Ras) have demonstrated anti-inflammatory, osteoprotective, and regenerative properties beyond glycemic control, suggesting potential applications in periodontal therapy. This systematic review aimed to evaluate the available preclinical evidence regarding the effects of GLP-1Ras on periodontal health, oral wound healing, and periodontal regeneration.*

Methods: *A systematic review was conducted according to the PRISMA 2020 guidelines. PubMed, ScienceDirect, and the Cochrane Library were searched from inception to June 2026. Experimental animal and in vitro studies evaluating GLP-1Ras on periodontal inflammation, oral wound healing, alveolar bone preservation, and periodontal regeneration were included. Methodological quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist.*

Results: *Three preclinical studies met the eligibility criteria, including one animal study and two in vitro investigations. Liraglutide and exendin-4 consistently reduced periodontal inflammation, suppressed pro-inflammatory cytokines, decreased osteoclast activity, preserved alveolar bone, enhanced osteogenic differentiation, promoted periodontal ligament cell proliferation and migration, and activated regenerative signaling pathways, including MAPK and Wnt signaling. All included studies demonstrated satisfactory methodological quality.*

Conclusion: *Current preclinical evidence suggests that GLP-1Ras possess significant anti-inflammatory, osteoprotective, and regenerative properties that may improve periodontal health and oral wound healing. However, the evidence is limited to experimental studies, and well-designed clinical trials are required to establish their efficacy and safety before routine application in periodontal practice.*

Introduction

Periodontitis is a chronic multifactorial inflammatory disease characterized by progressive destruction of the tooth-supporting tissues, including the gingiva, periodontal ligament, cementum, and alveolar bone. It results from a dysregulated host immune response to pathogenic oral biofilms, leading to clinical

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attachment loss, alveolar bone resorption, and eventual tooth loss if untreated [1]. Beyond oral health, periodontitis is strongly associated with systemic diseases, particularly type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease. Chronic hyperglycemia, oxidative stress, and persistent inflammation impair periodontal healing and accelerate tissue destruction, making diabetic patients more susceptible to severe periodontal disease [2].

Glucagon-like peptide-1 receptor agonists (GLP-1Ras), including liraglutide, exenatide, semaglutide, and dulaglutide, are widely used for the management of T2DM and obesity due to their glucose-lowering, weight-reducing, and cardioprotective effects. Beyond glycemic control, these agents exhibit anti-inflammatory, antioxidant, and immunomodulatory properties that extend to multiple tissues and organs [2,3].

Recent studies have highlighted the potential role of GLP-1Ras in periodontal therapy. GLP-1 receptors are expressed in periodontal and bone-related cells, suggesting that these agents may directly influence periodontal tissue homeostasis. Activation of GLP-1 signaling suppresses pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, while inhibiting NF-κB signaling and oxidative stress, thereby reducing periodontal inflammation and promoting tissue repair [3,4].

Preclinical studies have further demonstrated that GLP-1Ras may enhance periodontal regeneration by reducing osteoclast activity, preserving alveolar bone, promoting osteoblast differentiation, stimulating angiogenesis, and accelerating soft-tissue wound healing. Enhanced osteogenic differentiation of periodontal ligament stem cells through signaling pathways such as Wnt/β-catenin and MAPK further supports their regenerative potential [4]. However, current evidence is derived mainly from animal and in vitro studies with substantial variability in experimental models, interventions, and outcome measures, limiting direct comparison and clinical translation [5,6].

Periodontal regeneration and oral wound healing require coordinated regulation of inflammation, extracellular matrix remodeling, angiogenesis, and bone formation. Experimental evidence suggests that GLP-1Ras positively influence these processes by suppressing oxidative stress, reducing inflammatory mediators, enhancing osteoblast function, inhibiting osteoclastogenesis, and improving vascularization [7,8]. Recent reviews have also emphasized their promise as host-modulatory agents capable of improving periodontal outcomes through both metabolic and direct immunological mechanisms [9].

Despite these encouraging findings, the available preclinical evidence remains fragmented, and no systematic review has comprehensively synthesized the effects of GLP-1Ras on periodontal health, oral wound healing, and periodontal regeneration. Therefore, this systematic review aims to critically evaluate and summarize available in vitro and animal studies investigating these outcomes. By consolidating existing evidence, this review seeks to identify current knowledge gaps, evaluate the consistency of preclinical findings, and provide a foundation for future translational and clinical research in periodontal regenerative therapy [10].

Methods

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement. The review methodology was developed following the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.5) to ensure a transparent, reproducible, and comprehensive evidence synthesis.

Study Selection Process and Search Strategy

A comprehensive literature search was performed using PubMed, ScienceDirect, and the Cochrane Library from database inception to June 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to "GLP-1 receptor agonists," "liraglutide," "exenatide," "exendin-4," "semaglutide," "periodontitis," "periodontal disease," "oral wound healing," "alveolar bone loss," "periodontal regeneration," and "dental outcomes." Boolean operators (AND and OR)

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were used to optimize the sensitivity and specificity of the search strategy. In addition, the reference lists of eligible studies were manually screened to identify potentially relevant articles not captured during the electronic database search.

Eligibility Criteria

Studies were selected according to predefined eligibility criteria based on the Population, Intervention, Outcomes, Study Design, and Publication Characteristics. The eligibility criteria are summarized in Table 1.

Table 1. Predefined Eligibility Criteria for Included Studies

Domain	Inclusion Criteria	Exclusion Criteria
Population	Experimental animal models or in vitro periodontal cell models evaluating periodontal disease or oral wound healing.	Human studies without periodontal outcomes, non-periodontal disease models, reviews.
Intervention	GLP-1 receptor agonists including liraglutide, exendin-4, exenatide, semaglutide, or related agents.	Studies evaluating drugs other than GLP-1 receptor agonists.
Outcomes	Periodontal inflammation, inflammatory cytokines, osteogenic differentiation, alveolar bone loss, periodontal regeneration, wound healing, cellular proliferation and migration.	Studies without periodontal or oral healing outcomes.
Study Design	Experimental animal studies and in vitro laboratory studies.	Reviews, editorials, conference abstracts, case reports, letters, and duplicate publications.
Publication Characteristics	Peer-reviewed full-text articles published in English.	Non-English publications and articles without accessible full text.

Data Extraction

Data extraction was independently performed by two reviewers using a standardized data extraction form developed before study selection. Extracted variables included author, publication year, country, study design, experimental model, type of GLP-1 receptor agonist, sample characteristics, intervention protocol, evaluated outcomes, assessment methods, principal findings, and study conclusions. Any discrepancies between reviewers were resolved through discussion until consensus was achieved.

Quality Assessment

The methodological quality of the included studies was independently assessed by two reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist appropriate for the experimental study designs included in this review. The assessment evaluated methodological domains including appropriateness of the study design, clarity of research objectives, validity of the experimental model, reliability of outcome measurements, and appropriateness of statistical analyses. Disagreements between reviewers were resolved through discussion and consensus.

The quality assessment findings are summarized in Table 3, while the overall methodological quality and distribution of quality domains are presented in Figure 1 and Figure 2, respectively. Overall, all included studies fulfilled the major JBI quality assessment criteria, indicating satisfactory methodological quality suitable for qualitative evidence synthesis.

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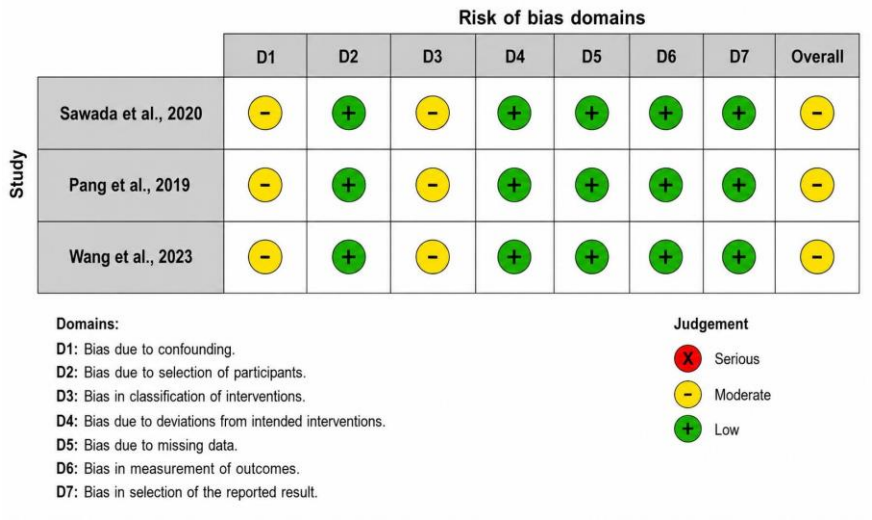


Figure 1: Traffic Light Plot of Risk of Bias Across Included Studies

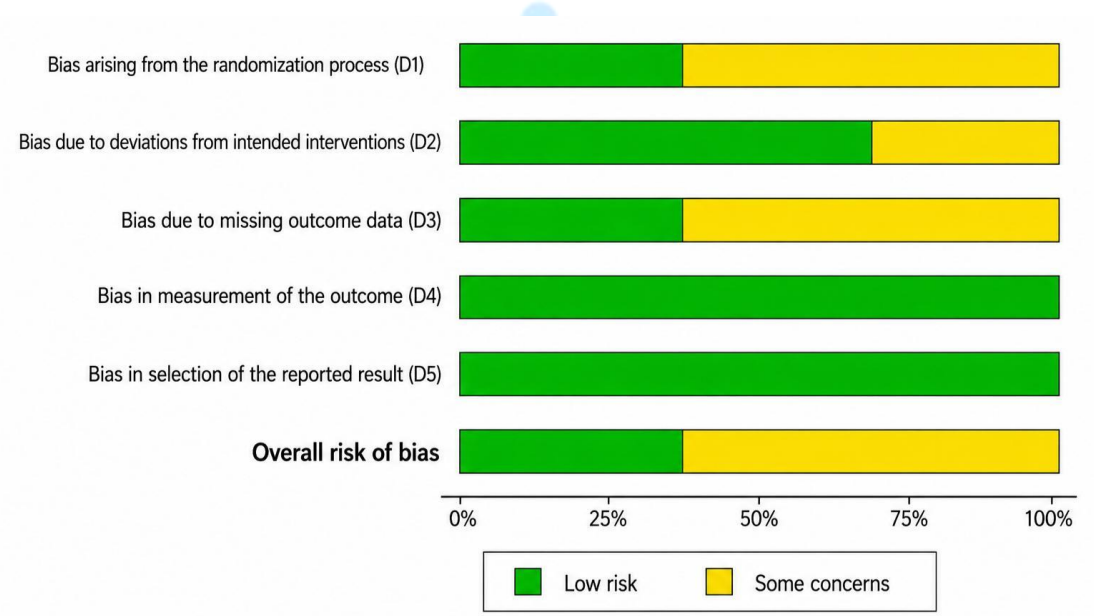


Figure 2: Risk of Bias Summary Across Included Studies

Results

Study Selection Process

Database searching identified a total of 1,160 records, including 512 records from PubMed, 386 from ScienceDirect, and 262 from the Cochrane Library. Following the removal of 206 duplicate records, 954 unique records remained for title and abstract screening. During this screening process, 764 records were excluded because they did not meet the predefined eligibility criteria. Consequently, 190 reports were sought for full-text retrieval, of which 22 reports could not be retrieved. The remaining 168 full-text articles were assessed for eligibility.

After full-text assessment, 165 studies were excluded because they did not satisfy the inclusion criteria, including not randomized controlled trials (n = 69), different intervention (n = 48), absence of the desired outcomes (n = 28), unrelated study population (n = 13), and

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review articles or editorials (n = 7). Finally, three studies fulfilled all eligibility criteria and were included in the qualitative synthesis of this systematic review (Figure 3).

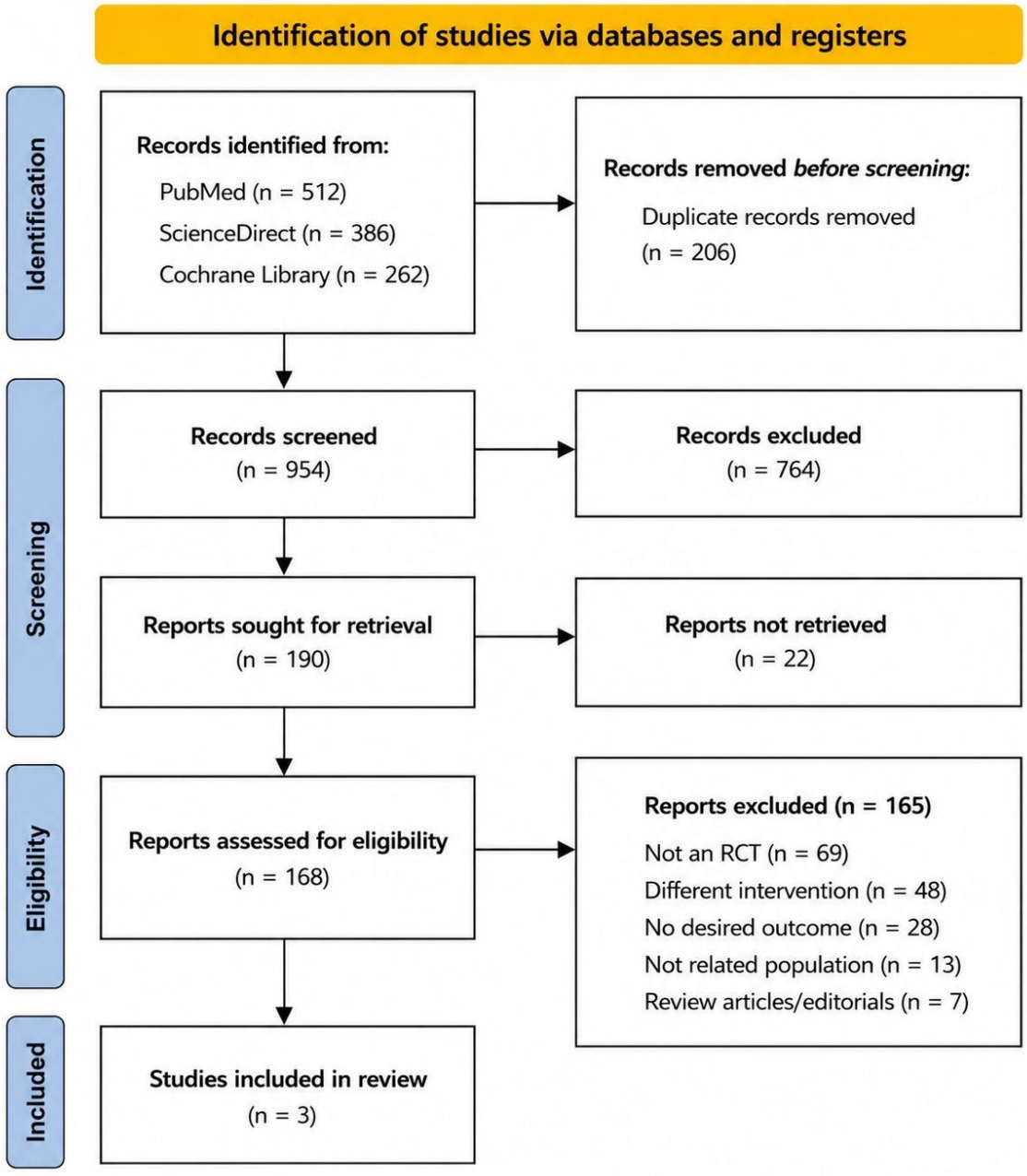


Figure 3: PRISMA Flow Diagram

Baseline Characteristics

The characteristics of the included studies are presented in Table 2. A total of three original experimental studies met the eligibility criteria and were included in this review. These comprised one animal study and two in vitro studies, providing preclinical evidence on the effects of glucagon-like peptide-1 receptor agonists (GLP-1Ras) on periodontal tissues. Geographically, one study was conducted in Japan, while the remaining two studies originated from China.

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The included studies evaluated two GLP-1 receptor agonists, namely liraglutide and exendin-4, using different experimental models. The animal study employed a ligature-induced periodontitis rat model to investigate the anti-inflammatory and bone-protective effects of liraglutide. In contrast, the in vitro studies examined the effects of liraglutide and exendin-4 on human periodontal ligament cells (hPDLCs) and human periodontal ligament stem cells (PDLSCs) cultured under inflammatory or hyperglycaemic conditions.

Across the included studies, outcome measures consistently focused on periodontal inflammation, osteogenic differentiation, cellular proliferation, migration, mineralization, inflammatory cytokine expression, and intracellular signaling pathways. Collectively, the findings demonstrated that GLP-1 receptor agonists reduced inflammatory responses, inhibited alveolar bone destruction, enhanced osteogenic differentiation, promoted periodontal tissue regeneration, and improved the biological functions of periodontal ligament cells. Furthermore, activation of molecular pathways such as MAPK and WNT signaling was associated with improved regenerative capacity under hyperglycaemic conditions.

Overall, the available preclinical evidence suggests that GLP-1 receptor agonists possess anti-inflammatory, osteoprotective, and regenerative properties, highlighting their potential as adjunctive therapeutic agents for improving periodontal health, enhancing oral wound healing, and optimizing postoperative dental outcomes. Nevertheless, the current evidence is primarily limited to experimental models, emphasizing the need for well-designed clinical studies to validate these findings and determine their translational relevance in routine dental practice.

Table 2. Characteristics of Included Studies

Author (Year)	Country	Study Design	Study Model/Population	Sample Size	GLP-1RA Intervention	Outcome Measures	Key Findings
Sawada et al. (2020)	Japan	Experimental animal study	Ligature-induced periodontitis in rats	30 rats	Liraglutide (0.03 mg/kg/day)	Gingival inflammation, TNF-α, iNOS, macrophage polarization, alveolar bone loss, osteoclast activity	Liraglutide significantly reduced periodontal inflammation, osteoclast formation, and alveolar bone loss.
Pang et al. (2019)	China	In vitro experimental study	Human periodontal ligament cells (hPDLCs)	Cells from 5 donors	Liraglutide (100 nM)	Cell proliferation, migration, osteogenic differentiation, IL-6, TNF-α, ALP, Runx2	Liraglutide enhanced proliferation, migration, mineralization, osteogenic differentiation, and reduced inflammatory cytokine expression.

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Wang et al. (2023)	China	In vitro experimental study	Human periodontal ligament stem cells (PDLSCs) cultured under normal and high-glucose conditions	PDLSCs isolated from healthy donors (18–26 years)	Exendin-4 (10 nM)	ALP staining, Alizarin Red staining, Runx2, ALP, Osx, MAPK signaling, WNT signaling	Exendin-4 restored osteogenic differentiation under high-glucose conditions by activating MAPK and WNT signaling pathways and increasing ALP, Runx2, and Osx expression.

Table 3. Methodological Quality Assessment of Included Studies Using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist

Study	Appropriate Study Design	Clear Objectives	Valid Experimental Model	Reliable Outcome Measurement	Appropriate Statistical Analysis	Overall Quality
Sawada et al. (2020)	✓	✓	✓	✓	✓	High
Pang et al. (2019)	✓	✓	✓	✓	✓	High
Wang et al. (2023)	✓	✓	✓	✓	✓	High

Outcomes

The primary outcomes assessed in the included studies are summarized in Table 4.

Primary Outcomes of the Included Studies

Study	Primary Outcome(s)	Assessment	Main Findings
Sawada et al. (2020)	Gingival inflammation; TNF-α; iNOS; macrophage polarization; osteoclast activity; alveolar bone loss	Histological and molecular analyses	Liraglutide reduced inflammation, osteoclast activity and alveolar bone loss.
Pang et al. (2019)	Cell proliferation; migration; osteogenic differentiation; ALP; Runx2; IL-6; TNF-α	Cell culture assays and molecular analyses	Liraglutide enhanced proliferation, migration and osteogenic differentiation while reducing inflammatory

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			cytokines.
Wang et al. (2023)	ALP staining; Alizarin Red staining; Runx2; Osx; MAPK and WNT signaling	In vitro functional and signaling assays	Exendin-4 restored osteogenic differentiation and activated regenerative signaling pathways under high-glucose conditions.

Overall, the included studies consistently demonstrated that GLP-1 receptor agonists exerted beneficial effects on periodontal tissues by reducing inflammation, promoting tissue regeneration, and enhancing osteogenic activity. Although the studies used different experimental models, the reported outcomes collectively support the therapeutic potential of GLP-1 receptor agonists in improving periodontal health and oral wound healing.

1. **Periodontal Inflammation**

All included studies evaluated inflammatory changes either directly or indirectly. Liraglutide significantly reduced inflammatory mediators, including TNF-α and iNOS, while decreasing inflammatory cell infiltration and macrophage activation. These findings indicate that GLP-1 receptor agonists suppress periodontal inflammation, which is one of the key mechanisms involved in the progression of periodontal disease. Reduced inflammation may facilitate a favorable environment for periodontal tissue repair.

2. **Osteogenic Differentiation and Bone Regeneration**

Two studies demonstrated enhanced osteogenic differentiation following GLP-1 receptor agonist treatment. Increased ALP activity, Runx2, Osx expression, and mineralized nodule formation suggested improved osteoblast differentiation and bone-forming capacity. These findings support the potential role of GLP-1 receptor agonists in promoting periodontal regeneration and preserving alveolar bone.

3. **Cellular Proliferation and Migration**

Improved proliferation and migration of periodontal ligament cells were consistently observed following liraglutide treatment. These biological processes are essential for periodontal tissue remodeling and wound healing, suggesting that GLP-1 receptor agonists may accelerate periodontal repair after tissue injury or dental procedures.

4. **Alveolar Bone Preservation**

The animal study demonstrated a marked reduction in osteoclast activity and alveolar bone loss following liraglutide administration. Preservation of alveolar bone is clinically important because progressive bone destruction is a hallmark of periodontitis and contributes to tooth loss.

5. **Molecular Signaling Pathways**

Wang et al. demonstrated activation of the MAPK and WNT signaling pathways following Exendin-4 treatment. These pathways regulate cell differentiation, proliferation, and tissue regeneration, providing mechanistic evidence that GLP-1 receptor agonists may enhance periodontal healing through modulation of intracellular signaling.

Collectively, the findings indicate that GLP-1 receptor agonists provide anti-inflammatory, osteoprotective, and regenerative effects on periodontal tissues. By reducing inflammation, preserving alveolar bone, enhancing osteogenic differentiation, and promoting cellular repair mechanisms, these agents show promising potential for improving periodontal health and supporting oral wound healing. However, because the current evidence is limited to animal and in vitro studies, well-designed human clinical trials are needed before these findings can be translated into routine dental practice.

Discussion

Summary of the Results

The present systematic review synthesized the available preclinical evidence regarding the effects

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of glucagon-like peptide-1 receptor agonists (GLP-1Ras) on periodontal health, oral wound healing, and postoperative dental outcomes. Three experimental studies met the eligibility criteria, including one animal study and two in vitro investigations. Despite differences in experimental models, all included studies consistently demonstrated that GLP-1Ras, particularly liraglutide and exendin-4, reduced periodontal inflammation, suppressed alveolar bone loss, enhanced osteogenic differentiation, improved periodontal ligament cell proliferation and migration, and promoted tissue regeneration. Collectively, these findings suggest that GLP-1Ras possess anti-inflammatory, osteoprotective, and regenerative properties that may have important applications in periodontal therapy and oral wound healing.

Comparison with Previous Literature

The findings of the present review are consistent with previous literature demonstrating the beneficial biological effects of GLP-1Ras on periodontal tissues. Sawada et al. first demonstrated that liraglutide significantly reduced inflammatory cell infiltration, TNF-α and iNOS expression, macrophage accumulation, osteoclast formation, and alveolar bone resorption in ligature-induced periodontitis, supporting its anti-inflammatory and bone-protective effects [11].

Similarly, recent reviews have reported that GLP-1Ras enhance periodontal tissue regeneration by stimulating osteogenic differentiation of periodontal ligament stem cells through activation of the MAPK and Wnt/β-catenin signaling pathways while simultaneously suppressing oxidative stress and inflammatory cytokines [12,13].

Furthermore, emerging evidence suggests that the beneficial effects of GLP-1Ras extend beyond glycemic control. Their pleiotropic anti-inflammatory and immunomodulatory properties may reduce periodontal tissue destruction, improve bone remodeling, and enhance peri-implant healing, particularly in patients with type 2 diabetes mellitus [12,14].

Our findings also agree with recently published scoping and narrative reviews, which concluded that although current evidence is predominantly preclinical, GLP-1Ras demonstrate considerable potential as adjunctive agents in periodontal and implant therapy. However, these reviews similarly emphasized the limited availability of well-designed human clinical studies, preventing definitive clinical recommendations [12,15].

Clinical Implications

The present findings suggest that GLP-1 receptor agonists may represent a promising adjunctive therapeutic strategy for managing periodontal diseases, particularly in patients with diabetes mellitus who experience impaired wound healing and increased periodontal destruction. By suppressing inflammatory mediators, preserving alveolar bone, enhancing periodontal ligament cell function, and stimulating regenerative signaling pathways, GLP-1Ras may improve periodontal regeneration and postoperative healing following dental surgical procedures. Nevertheless, current evidence remains insufficient to recommend their routine clinical use in dentistry because available data are primarily derived from animal and laboratory studies rather than randomized clinical trials.

Limitations

Several limitations should be acknowledged. First, only three eligible studies were identified, limiting the overall strength of evidence. Second, all included investigations were preclinical studies involving either animal models or in vitro experiments, restricting direct translation of the findings to clinical practice. Third, considerable heterogeneity existed regarding experimental models, GLP-1RA formulations, outcome measures, and laboratory methodologies, precluding quantitative meta-analysis. Finally, no long-term human clinical trials evaluating periodontal or postoperative dental outcomes following GLP-1RA therapy were available.

Future Directions

Future research should prioritize well-designed randomized controlled clinical trials evaluating

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the effects of GLP-1Ras on periodontal disease progression, oral wound healing, implant success, and postoperative recovery. Comparative studies involving newer GLP-1Ras such as semaglutide, dulaglutide, and tirzepatide are also warranted. In addition, mechanistic investigations exploring inflammatory signaling pathways, angiogenesis, osteogenesis, and interactions with the oral microbiome may further clarify the biological mechanisms underlying the beneficial effects of GLP-1Ras on periodontal tissues.

Conclusion

In conclusion, the available preclinical evidence suggests that GLP-1 receptor agonists exert significant anti-inflammatory, osteoprotective, and regenerative effects on periodontal tissues. These agents reduce periodontal inflammation, preserve alveolar bone, enhance osteogenic differentiation, and promote periodontal tissue repair, indicating their potential role as adjunctive therapies in periodontology and postoperative dental care. However, because the current evidence is limited to experimental animal and in vitro studies, robust human clinical trials are essential before GLP-1Ras can be incorporated into routine periodontal treatment protocols.

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