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Review

Beyond Glycemic Control: Periodontal, Salivary, and Oral Microbiome Effects of GLP-1 Receptor Agonists—A Scoping Review of Clinical and Preclinical Evidence

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Abstract

Background/Objectives: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used to treat type 2 diabetes and obesity, yet their periodontal, peri-implant, salivary, and oral microbial effects remain incompletely characterized. This scoping review mapped the clinical and preclinical evidence on GLP-1RA-related oral effects, investigated mechanisms, and knowledge gaps. **Methods:** PubMed, Scopus, and the Web of Science Core Collection were searched from inception to 9 September 2026. Original human, animal in vivo, in vitro/ex vivo, and mixed-design studies were eligible when a GLP-1RA was a principal intervention or exposure and a relevant oral or orofacial outcome was reported. Two reviewers independently screened records. Study characteristics, interventions, outcomes, and findings were charted and synthesized descriptively. The review followed Joanna Briggs Institute methodology and PRISMA-ScR guidance and was registered on the Open Science Framework after study selection but before completion of the methodological appraisal and manuscript. **Results:** Twenty-seven publications were included, 23 of which were wholly or partly preclinical. Four publications were exclusively human, and one mixed-design publication included an additional human observational component. Experimental findings suggested anti-inflammatory, antioxidant, and osteogenic effects, but molecular responses were not consistently accompanied by structural benefits. Evidence concerning salivary function, oral microbial changes, and orofacial adverse events was limited and heterogeneous. Human findings were derived from non-randomized observational and descriptive designs. **Conclusions:** Evidence of potential oral effects is predominantly experimental, and human data are insufficient to establish clinical benefit or causality. Prospective controlled studies with standardized clinical outcomes are needed to determine whether experimental findings translate into meaningful oral-health benefits.

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1. Introduction

The increasing burden of diabetes and obesity provides the clinical context for the expanding use of glucagon-like peptide-1 receptor agonists (GLP-1RAs). In 2021, an estimated 529 million people worldwide were living with diabetes, with the number projected to exceed 1.31 billion by 2050 [1]. Global estimates also indicate that more than one billion people were living with obesity in 2022 [2].

Initially developed for type 2 diabetes, GLP-1RAs improve glycemic control through glucose-dependent insulin secretion, glucagon suppression, and delayed gastric emptying, while also reducing appetite and body weight. Evidence of cardiovascular benefit and efficacy in obesity has subsequently expanded their therapeutic relevance beyond glucose regulation, establishing GLP-1RAs as important systemic cardiometabolic therapies [3–6].

This expanding therapeutic reach makes it increasingly important to investigate effects in tissues and organs that were not the primary focus of early clinical trials. The oral cavity is especially relevant because it is simultaneously exposed to metabolic disturbance, microbial challenge, inflammatory injury, and continuous tissue remodeling. Periodontal tissues, salivary glands, the oral microbiome, and the bone–implant interface may therefore respond to both the direct biological actions of GLP-1 receptor activation and the indirect consequences of improved glycemic control, weight reduction, altered dietary behavior, and decreased systemic inflammation. Distinguishing these pathways is essential: an oral change observed during GLP-1RA therapy may represent a receptor-mediated tissue response, a consequence of improved metabolic health, an adverse effect of treatment, or an interaction among these mechanisms [1,7,8].

Persistent hyperglycemia may amplify periodontal injury through several interconnected pathways. Advanced glycation end products and their receptor-mediated signaling promote oxidative stress, endothelial dysfunction, cytokine production, altered immune-cell activity, impaired collagen turnover, and defective resolution of inflammation [9]. Diabetes may also impair neutrophil function, macrophage responses, microvascular homeostasis, osteoblast activity, and bone remodeling, thereby weakening periodontal repair and increasing susceptibility to progressive tissue destruction [10]. Obesity is also associated with macrophage accumulation and increased expression of inflammatory mediators in adipose tissue [11]. Because GLP-1RAs improve several of these metabolic abnormalities, favorable periodontal outcomes during treatment may arise even in the absence of a direct pharmacological action within periodontal tissues.

Experimental evidence supports the biological plausibility of direct oral effects mediated by GLP-1 receptor signaling, particularly through anti-inflammatory, cytoprotective, and bone-remodeling pathways. However, receptor distribution and cellular specificity in oral tissues remain incompletely defined, and direct pharmacological actions cannot yet be clearly separated from systemic metabolic effects. Moreover, favorable changes in molecular biomarkers should not be interpreted as evidence of clinically meaningful prevention of periodontal destruction [4,12–14].

GLP-1 receptor activation may also influence osteogenic differentiation and oral tissue regeneration. Because hyperglycemia impairs progenitor-cell function and bone repair, the reported pro-osteogenic and cytoprotective actions of GLP-1RAs suggest potential regenerative effects within metabolically compromised periodontal and alveolar environments [15–18].

The potential relevance of GLP-1RAs also extends to implant therapy, where successful osseointegration depends on a coordinated interaction between inflammatory resolution, vascular responses, extracellular-matrix formation, and bone remodeling. Diabetes can disturb this balance, particularly in the presence of poor glycemic control, thereby compromising peri-implant healing and long-term tissue stability. In experimental diabetic models, exenatide and liraglutide enhanced peri-implant osteogenesis, bone microarchitecture, and bone–implant integration, providing a biological rationale for a possible beneficial effect. A retrospective clinical study also reported lower marginal bone loss among patients receiving GLP-1-based medication than among those treated with insulin or metformin. Although clinically intriguing, these findings remain preliminary and do not establish that GLP-1RA therapy independently improves implant outcomes [10,19,20].

The potential oral consequences of GLP-1RA exposure are not necessarily limited to periodontal inflammation and bone metabolism. Saliva is essential for lubrication, mucosal integrity, taste, swallowing, antimicrobial defense, buffering, remineralization, and maintenance of microbial homeostasis. Changes in salivary function may therefore affect several oral outcomes simultaneously, including discomfort, dietary behavior, caries susceptibility, mucosal disease, plaque accumulation, and quality of life. A small human case series described severe oral dryness and reduced salivary secretion temporally associated with semaglutide treatment for weight management. A subsequent pharmacovigilance analysis identified disproportionate reporting signals for dry mouth and dysgeusia with semaglutide and for dysgeusia with other GLP-1RAs, although spontaneous-report data cannot establish incidence or causality. Conversely, exendin-4 improved salivary secretion and reduced salivary-gland injury in a D-galactose-induced experimental aging model. These findings highlight the possibility of molecule-specific, context-dependent, or indirect salivary effects and emphasize the need to distinguish subjective xerostomia from objectively measured hyposalivation [21–24].

The oral microbiome may represent an additional link between GLP-1RA therapy and oral health. Metabolic, inflammatory, dietary, and salivary changes associated with diabetes, obesity, and their treatment may alter oral microbial ecology. However, whether GLP-1RAs directly modify oral microbial communities or act indirectly through improved metabolic and immune homeostasis remains uncertain [7,10,25,26].

Previous reviews have characterized periodontal inflammation, bone remodeling, and regeneration in relation to GLP-1-based therapies [27,28]. Some syntheses have also incorporated endogenous incretin profiles and pathways involving dipeptidyl peptidase-4 (DPP-4) [29,30], while narrative reviews have discussed broader oral-health implications and considerations for dental care [31,32]. These reviews address overlapping questions but differ in their intervention definitions, eligibility criteria, and outcome coverage, limiting direct comparison of the evidence available across oral-health domains.

A remaining need is to integrate original studies in which a GLP-1RA is a principal intervention or exposure across periodontal, regenerative, peri-implant, salivary, oral microbial, and orofacial adverse-event domains. Such a synthesis can distinguish evidence arising from pharmacological exposure from investigations limited to endogenous incretin levels or DPP-4-related biology, while separating experimental mechanisms from patient-level observations. This distinction is essential because favorable molecular findings do not establish clinical benefit, and observational associations or pharmacovigilance signals alone do not establish causality.

Accordingly, this scoping review aimed to map and critically characterize original clinical and preclinical evidence across these oral-health domains, examining differences among agents, study designs, and experimental contexts. The scoping approach was selected to characterize the extent, distribution, and heterogeneity of the evidence and identify translational gaps,

rather than to estimate treatment efficacy. A complementary exploratory bibliometric analysis examined the thematic and geographical structure of the included literature.

2. Materials and Methods

2.1. Review Design and Protocol

This scoping review was conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews and reported in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) [33], with additional reporting elements cross-checked against the PRISMA 2020 statement. The protocol was registered on the Open Science Framework after completion of study selection and preliminary data charting, but before completion of the design-specific methodological appraisal and finalization of the manuscript (OSF DOI: 10.17605/OSF.IO/MHK9U). The timing of registration and the review procedures completed before registration were transparently documented in the registered record.

The review was designed to map the extent, characteristics, and principal findings of the clinical and preclinical evidence concerning the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on periodontal and peri-implant tissues, salivary function, oral microbial communities, and other directly relevant oral or orofacial outcomes. The primary review question was: What clinical and preclinical evidence is available regarding the effects of GLP-1RAs on periodontal and peri-implant tissues, salivary function, oral microbial communities, and other clinically relevant oral or orofacial outcomes?

The review question was structured according to the Population–Concept–Context framework. The population encompassed human participants, experimental animals, and oral or dental cellular and tissue models; the concept comprised intervention with or exposure to a GLP-1RA; and the context included periodontal, peri-implant, salivary, oral microbiological, and other directly relevant oral-health settings. An adapted Population–Intervention–Comparator–Outcomes–Study design framework was additionally used to operationalize the eligibility criteria consistently across human, animal in vivo, in vitro/ex vivo, and mixed-design studies.

2.2. Information Sources and Search Strategy

A systematic literature search was conducted in PubMed, Scopus, and the Web of Science Core Collection from database inception to 9 September 2026. A common combination of free-text terms and Boolean operators was used across all three databases, with field codes and syntax adapted to the requirements of each platform.

The search comprised two conceptual blocks: terms identifying GLP-1RAs and terms identifying periodontal, salivary, peri-implant, or oral microbiome outcomes. The complete core search strategy was: (“GLP-1 receptor agonist*” OR “glucagon-like peptide-1 receptor agonist*” OR “glucagon like peptide 1 receptor agonist*” OR GLP-1RA* OR GLP1RA* OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR lixisenatide OR albiglutide) AND (periodont* OR gingiv* OR “periodontal disease*” OR “periodontal inflammation” OR “periodontal tissue*” OR “periodontal ligament” OR “oral health” OR “oral microbiom*” OR “oral microbiota” OR “subgingival microbiom*” OR “subgingival microbiota” OR “dental plaque” OR “subgingival plaque” OR saliva* OR xerostomi* OR hyposalivat* OR “dry mouth” OR “salivary flow” OR peri-implant* OR periimplant* OR “alveolar bone”).

Searches were restricted, where database filtering options permitted, to English-language records indexed as articles. Publication type and full-text language were subsequently verified during study selection. These filters were intended to prioritize original research and may have limited the retrieval of review articles. No restrictions were applied regarding publication year, participant age, geographical location, or experimental model.

Individual drug names were incorporated to identify studies that did not explicitly use the broader GLP-1RA terminology. Review articles were ineligible for the evidence synthesis, irrespective of publication date, but were considered separately as contextual sources for the rationale and discussion. The complete database-specific search strategies, including platform-specific syntax, field codes, applied limits, search dates, and retrieval counts, are provided in Supplementary Table S1. Exendin-4 was not included as a separate search term, although publications investigating this agent were identified and included. No supplementary search incorporating this term was performed, and its potential additional yield was not assessed.

2.3. Eligibility Criteria and Study Selection

Eligibility criteria were operationalized using an adapted Population–Intervention–Comparator–Outcomes–Study design (PICOS) framework to accommodate the heterogeneous clinical and preclinical evidence base.

- Population (P): Human participants exposed to GLP-1RA therapy, irrespective of treatment indication, as well as experimental animals and oral or dental cellular and tissue models relevant to periodontal, peri-implant, salivary, microbiological, or other directly related oral-health outcomes. Populations and models with diabetes, hyperglycemia, obesity, metabolic dysfunction, periodontal disease, or peri-implant conditions were of particular interest, although the presence of metabolic disease was not required for eligibility.
- Intervention (I): Systemic or local administration, exposure, or experimental evaluation of a GLP-1RA as a principal study factor. Eligible agents included liraglutide, semaglutide, exenatide, exendin-4, dulaglutide, lixisenatide, and albiglutide, as well as GLP-1 receptor activation achieved through experimental delivery systems. Studies involving multi-receptor agonists were eligible only when GLP-1RA-specific oral findings could be distinguished from the effects of other interventions.
- Comparator (C): Placebo, vehicle, untreated or healthy controls, disease controls, alternative glucose-lowering therapies, active experimental comparators, or different GLP-1RA doses, formulations, administration routes, or exposure durations. A comparator was not mandatory when the study otherwise provided eligible original evidence, as in case reports, case series, or pharmacovigilance analyses.
- Outcomes (O): Eligible outcomes included periodontal inflammation and tissue destruction; gingival and periodontal biomarkers; inflammatory cytokines, matrix metalloproteinases, and oxidative-stress markers; alveolar bone loss, microarchitecture, and remodeling; osteogenic and osteoclastic activity; periodontal ligament, dental pulp, or bone-marrow stem-cell responses; peri-implant osseointegration and marginal bone changes; salivary flow, salivary-gland function, xerostomia, or hyposalivation; oral or subgingival microbiome composition; and clinically relevant oral or orofacial manifestations and adverse events.
- Study design (S): Eligible publications comprised original human clinical or observational research, including cohort, case–control, registry-based, pharmacovigilance, case-series, and case-report studies; animal in vivo investigations; in vitro or ex vivo studies using eligible oral or dental cells or tissues; and mixed-design investigations combining in vitro, ex vivo, animal, or human components.

Studies were included when a GLP-1RA represented a principal intervention, exposure, or experimental factor and at least one eligible periodontal, peri-implant, salivary, microbiological, oral, or orofacial outcome was reported. Studies conducted under non-diabetic conditions remained eligible when they provided relevant mechanistic evidence concerning oral tissues or GLP-1 receptor activation. Metabolic and diabetic status was recorded during data charting and considered when interpreting the applicability of the findings.

Studies were excluded for any of the following reasons:

- Evidence syntheses, including narrative, systematic, or scoping reviews, meta-analyses, and bibliometric analyses;
- Editorials, commentaries, protocols, guidelines, corrections, corrigenda, or letters without original data;
- Publications not written in English;
- Absence of original results;
- Absence of an eligible periodontal, peri-implant, salivary, oral microbiome, oral, or orofacial outcome;
- Absence of a GLP-1RA as a principal intervention, exposure, or experimental factor;
- Evaluation of another antidiabetic medication without a distinct GLP-1RA intervention or exposure group;
- Use of the term "oral" exclusively to denote the route of drug administration;
- Use of the salivary glands exclusively as a drug-delivery or gene-therapy site without assessment of salivary or oral outcomes; or
- General skeletal, calvarial, or bone-regeneration research lacking a direct dental, periodontal, alveolar, or peri-implant context.

All retrieved records were imported into Rayyan and consolidated into a single review database. Potential duplicates were identified using Rayyan and verified through hierarchical comparison of the DOI, PMID, and normalized article title. DOI normalization involved removing URL prefixes, converting characters to lowercase, and eliminating terminal punctuation. Titles were normalized by harmonizing capitalization, punctuation, spacing, and typographical characters. Duplicate decisions were manually confirmed before screening.

Two reviewers (RD and VB) independently screened titles and abstracts against the predefined eligibility criteria. Records judged potentially eligible or insufficiently documented at this stage were retained for full-text assessment. The same reviewers subsequently evaluated the retrieved full texts and assigned one primary exclusion reason to each ineligible report. Disagreements at either stage were resolved through discussion and consensus. Reviews and other non-original publications retrieved despite application of the article filter were excluded during screening. The numbers of identified, deduplicated, screened, excluded, and included records, together with the reasons for exclusion following full-text assessment, are reported in the PRISMA 2020 flow diagram (Figure 1) [34].

2.4. Data Charting and Methodological Appraisal

A standardized data-charting form was developed specifically for this review. To ensure consistent application across the heterogeneous evidence base, RD and VB independently applied the form to four studies representing the human, animal in vivo, in vitro/ex vivo, and mixed-design categories. Differences in interpretation were discussed, and the charting instructions were clarified before full data charting and verification. Data were charted by RD and VB and independently verified by AG. Discrepancies were resolved through consultation of the full-text reports and discussion until consensus was reached. Information unavailable in the original publications was recorded as "not reported" and was not inferred from secondary sources.

Extracted information comprised bibliographic characteristics; study design and evidence category; population, biological material, or experimental model; metabolic status; sample size, experimental groups, and comparators; and the investigated GLP-1RA, including dose, formulation, administration route, treatment frequency, and exposure duration. Oral-health variables encompassed periodontal, peri-implant, salivary, cellular, tissue, and microbiome models, together with the corresponding clinical, radiographic, histological, microbiological, biochemical, cellular, and molecular outcomes. Data on inflammatory me-

diators, matrix metalloproteinases, oxidative-stress and immune responses, osteogenic and osteoclastic pathways, bone-remodeling indices, salivary function, microbial alterations, and oral or orofacial adverse events were also charted. Statistical methods, principal findings, direction of effect, funding sources, and declared conflicts of interest were recorded.

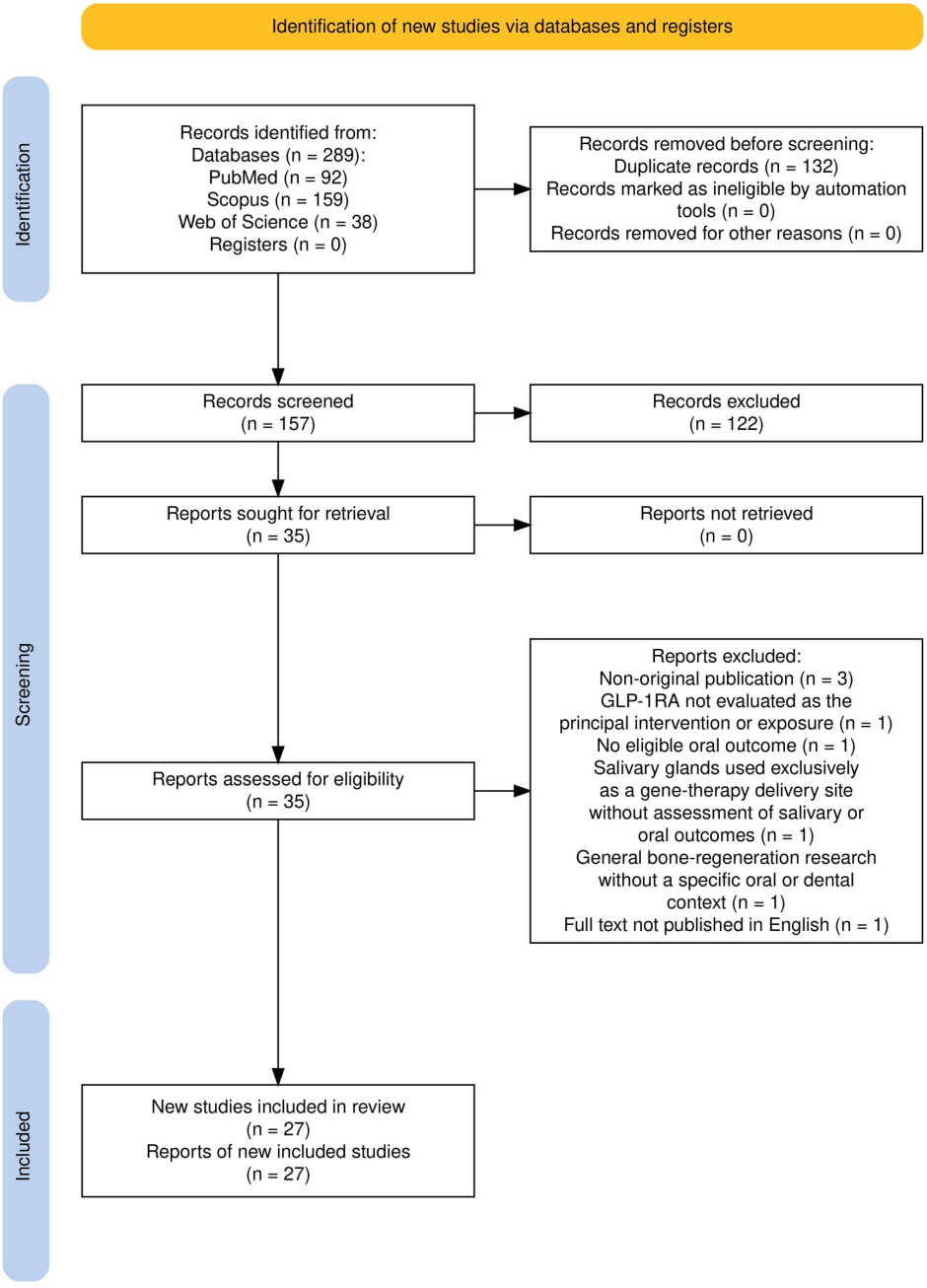


Figure 1. PRISMA 2020 Flow Diagram of Study Identification, Screening, Eligibility Assessment, and Inclusion.

Mixed-design publications were counted once in the overall evidence base, while their human, animal, in vitro, and ex vivo components were charted separately to preserve their distinct methodological characteristics and outcomes.

A design-specific methodological appraisal was undertaken to support interpretation of the mapped evidence. Human studies were evaluated using the Joanna Briggs Institute critical-appraisal checklist appropriate to each design, animal in vivo studies using the SYRCLE risk-of-bias tool, and in vitro dental studies using the QUIN tool. Components of mixed-design publications were assessed separately with the corresponding instrument.

JBI items were recorded as "yes", "no", "unclear", or "not applicable"; SYRCLE domains were classified as presenting a low, high, or unclear risk of bias; and QUIN assessments were scored and interpreted according to the instrument-specific guidance. Two reviewers performed the assessments independently and resolved disagreements through discussion and consensus. Because the instruments evaluate different methodological constructs, their findings were synthesized separately and were not combined into a single overall score. Methodological appraisal did not determine study eligibility but was used to contextualize the reliability, limitations, and translational relevance of the evidence.

2.5. Evidence Classification and Synthesis

The included publications were assigned to one of four predefined evidence categories: human clinical or observational studies, animal in vivo investigations, in vitro or ex vivo studies, and mixed-design investigations combining two or more methodological components. Mixed-design publications were classified at the publication level, while their individual components were considered separately during data charting and interpretation.

Evidence was organized according to the investigated GLP-1RA, population or experimental model, metabolic context, oral-health domain, comparator, evaluated outcomes, and proposed biological mechanisms. The synthesis encompassed periodontal inflammation and tissue destruction, oxidative stress, alveolar bone remodeling, osteogenic and osteoclastic activity, periodontal ligament and dental pulp stem-cell responses, peri-implant osseointegration, salivary dysfunction, oral or orofacial adverse events, and oral microbiome alterations. Reported effects were interpreted in relation to the relevant comparators, statistical findings, and methodological context of each study.

Quantitative meta-analysis was not undertaken because the evidence-mapping objective of the review and substantial heterogeneity in study designs, biological models, interventions, comparators, treatment protocols, and outcome definitions precluded meaningful statistical pooling. Findings were therefore synthesized descriptively using evidence tables, frequency distributions, and a structured narrative approach. Human, animal in vivo, in vitro/ex vivo, and mixed-design evidence streams were presented according to their respective methodological contexts and integrated to identify convergent findings, divergent results, and evidence gaps. Mechanistic and preclinical findings were interpreted as evidence of biological plausibility and were not extrapolated directly to clinical effectiveness or causality.

2.6. Bibliometric Analysis

A complementary exploratory bibliometric analysis was conducted using metadata from the 27 publications included in the final evidence synthesis. Records retrieved from PubMed, Scopus, and the Web of Science Core Collection were consolidated using DOI, PMID, and normalized article title as matching identifiers. When a publication was indexed in more than one database, the corresponding records were reconciled to obtain the most complete author-keyword and affiliation data while preserving the terminology reported in the original publication.

Bibliometric networks were constructed and visualized using VOSviewer version 1.6.20. The conceptual structure of the evidence base was examined through author-keyword co-occurrence analysis using full counting and association-strength normalization. Given the limited size and terminological diversity of the corpus, the minimum occurrence threshold was set at one. Publications without author-supplied keywords did not contribute terms to this analysis. A thesaurus file was used to harmonize differences in capitalization, hyphenation, spelling, and singular or plural forms. Terms representing distinct pharmacological agents or experimental agonists—including liraglutide, semaglutide, exenatide, and exendin-4—were retained as separate nodes. Node size represented keyword occurrence,

links indicated co-occurrence within the same publication, and link strength reflected the frequency of these relationships.

Geographical distribution and international collaboration were examined using country information derived from all author affiliations reported for each publication. Country-name variants were standardized before analysis, and affiliation assignments were verified against the source publications when exported metadata were incomplete or inconsistent. A country-level co-authorship network was generated using full counting, fractionalization normalization, and a minimum threshold of one publication per country. Under full counting, each country received one publication credit for every article in which it appeared, irrespective of the number of contributing authors or affiliations from that country; consequently, the sum of country-level publication counts could exceed the number of included publications. Links represented co-authorship between countries within the same publication, whereas countries without international co-authorship remained unconnected. Overlay visualization was used to represent the average publication year associated with each country.

Because the analysis was based on a small and methodologically heterogeneous corpus, both networks were interpreted descriptively as exploratory representations of thematic structure, geographical distribution, international collaboration, and temporal development. Node size, link strength, network position, and average publication year were not interpreted as measures of scientific quality, clinical importance, or comparative research performance.

3. Results

3.1. Study Selection

The database searches identified 289 records: 92 from PubMed, 159 from Scopus, and 38 from the Web of Science Core Collection. After 132 duplicate records were removed, 157 unique records underwent title and abstract screening, of which 122 were excluded. The full texts of the remaining 35 reports were retrieved and assessed for eligibility. Eight reports were excluded following full-text assessment. The primary reasons for exclusion are summarized in Figure 1, while the individual excluded reports and the corresponding primary reason for exclusion are provided in Supplementary Table S2. Consequently, 27 studies met the eligibility criteria and were included in the final evidence synthesis.

3.2. Characteristics of the Included Evidence

The 27 included publications were published between 2015 and 2026 and constituted a methodologically heterogeneous evidence base. Four were exclusively human clinical or observational studies, eight were animal in vivo investigations, four were in vitro or ex vivo studies, and eleven employed mixed designs integrating two or more methodological components. Overall, 23 publications (85.2%) were exclusively preclinical or incorporated at least one preclinical component.

Liraglutide and exendin-4 were the most frequently investigated agents, whereas semaglutide and exenatide were represented less extensively. Human database-based investigations additionally evaluated several marketed GLP-1-based therapies, including dulaglutide and the dual GIP/GLP-1 receptor agonist tirzepatide, in comparative exposure or safety analyses. The evidence encompassed periodontal inflammation and tissue destruction, alveolar bone loss and remodeling, osteogenic differentiation and periodontal regeneration, peri-implant bone formation and osseointegration, salivary dysfunction and hyposalivation, oral and peri-implant microbial alterations, and oral or orofacial adverse-event signals. Considerable heterogeneity was observed across experimental models, metabolic conditions, interventions, administration protocols, comparators, outcome definitions, and analytical methods. The methodological characteristics and principal findings of the included publications are summarized in Table 1.

Table 1. Design Characteristics, Experimental Models, Interventions, Outcomes, and Principal Findings of the Included Studies.

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Yang M. et al. [35]	2022	Anti-inflammatory, glycemic, osteoprotective, and osteogenic effects of liraglutide in experimental diabetes-associated periodontitis.	Randomized controlled animal in vivo study.	46 male Wistar rats with high-fat-diet and low-dose streptozotocin-induced type 2 diabetes and ligature-induced periodontitis. Four groups: control, $n = 8$; liraglutide only, $n = 8$; diabetic periodontitis plus saline, $n = 15$; and diabetic periodontitis plus liraglutide, $n = 15$.	Intraperitoneal liraglutide, 300 μg/kg/day for 4 weeks. Comparators were untreated healthy controls, healthy rats receiving liraglutide, and rats with diabetic periodontitis receiving 0.9% saline.	Fasting blood glucose, body weight, and oral glucose tolerance; serum IL-6, TNF-α, and IL-1β measured by ELISA; periodontal histology using hematoxylin–eosin staining; alveolar bone resorption and microarchitecture assessed by morphometry and micro-CT; RANKL and OPG expression evaluated by immunohistochemistry; and gingival Runx2 and ALP mRNA expression measured by qRT-PCR.	Data were reported as mean ± SD and compared using one-way ANOVA in SPSS. Statistical significance was set at $p < 0.05$. The full text did not report the SPSS version, post hoc procedure, assumption testing, or adjustment for multiple comparisons.	Compared with saline-treated rats with diabetic periodontitis, liraglutide reduced fasting blood glucose, serum IL-6, TNF-α, and IL-1β levels, periodontal inflammatory infiltration, and alveolar bone resorption. It improved alveolar bone microarchitecture, decreased the RANKL/OPG ratio, and increased gingival Runx2 and ALP mRNA expression ($p < 0.05$). These findings support anti-inflammatory and osteoprotective effects in this animal model but do not establish clinical efficacy in humans.
Khan F.I. et al. [23]	2025	Oral/otolaryngologic adverse-event signals associated with GLP-1RAs, including dry mouth and dysgeusia.	Retrospective pharmacovigilance study (FAERS).	9746 otolaryngologic adverse-event reports associated with GLP-1 receptor agonists in FAERS (data through 2023).	Exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide; spontaneous reports.	FAERS disproportionality analysis by adverse-event category.	Descriptive counts and pharmacovigilance disproportionality analysis using reporting odds ratios (RORs) and proportional reporting ratios (PRRs), with 95% confidence intervals. A signal was defined by PRR ≥ 2 and a lower 95% CI bound for the ROR > 1.	Semaglutide showed signals for dry mouth and dysgeusia; liraglutide and exenatide showed dysgeusia signals. Findings indicate reporting signals, not incidence or causality.
Mawardi H.H. et al. [22]	2023	Hyposalivation temporally associated with semaglutide.	Human case series.	Three women with semaglutide-associated hyposalivation; median age 34 years (range 27–46).	Semaglutide used for weight loss; mean exposure 11.3 weeks (range 6–16).	Clinical oral examination and modified Schirmer test.	Descriptive case-series analysis only; no inferential statistical testing was performed.	Severe oral dryness and minimal frothy saliva were reported. Mean modified Schirmer result: 9 mL at 3 min (range 8–10 mL; unit reproduced from the source; see note). Clinical improvement followed individualized management.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Sawada N. et al. [12]	2020	Anti-inflammatory and anti-resorptive effects of liraglutide in experimental periodontitis.	Randomized animal in vivo experiment.	Thirty male Sprague-Dawley rats initially assigned to control, ligature-induced periodontitis, or periodontitis plus liraglutide groups. Owing to attrition, systemic analyses included $n = 8$, 8, and 7, respectively; outcome-specific samples ranged from $n = 3$ to 10.	Liraglutide for 2 weeks versus untreated ligature-induced periodontitis and normal controls.	Histology, gingival inflammatory-gene expression, macrophage phenotyping, micro-CT, and osteoclast assessment.	Sample size was estimated using G*Power 3.1. Data were expressed as mean ± SEM and analyzed by one-way ANOVA followed by Bonferroni correction for multiple comparisons; $p < 0.05$ was considered significant.	Liraglutide reduced inflammatory infiltration, macrophage accumulation, TNF-α/iNOS expression, M1 macrophages, osteoclasts, and ligature-induced alveolar bone resorption.
Wang, Y et al. [19]	2024	Effects of liraglutide on osteogenesis of alveolar BMSCs and implant osseointegration under diabetes.	Mixed human-cell in vitro and rat in vivo study.	Human alveolar BMSCs from 20 participants (10 insulin-treated patients with T2DM and 10 matched non-diabetic controls); 16 male rats (8 Wistar and 8 Goto-Kakizaki), allocated to four groups ($n = 4$/group). In vitro assays were repeated in at least three independent experiments.	Liraglutide concentration-response in BMSCs; liraglutide after implant placement in rats.	ALP activity/staining, ARS, RT-PCR, Western blotting, micro-CT, and toluidine-blue histology.	Data were expressed as mean ± SD and analyzed using Student's *t*-test or two-way ANOVA in GraphPad Prism 5.0; $p < 0.05$ was considered significant.	Liraglutide enhanced osteogenesis through BMP2/Smad/Runx2; 10^{-8} mol/L was optimal and $>10^{-7}$ mol/L was detrimental. It improved peri-implant bone formation and integration in Wistar and GK rats.
Shen, YF et al. [36]	2026	Roles of GLP1R/GIPR signaling in PDLSC maintenance, differentiation, and periodontal regeneration.	Mixed mechanistic in vitro, mouse in vivo, and human cross-sectional survey study.	Human periodontal tissues/PDLSCs from 10 donors (5 healthy and 5 with periodontitis); clinical survey of 150 patients with periodontitis, including 74 GLP1R or dual GLP1R/GIPR agonist users; 120 wild-type C57BL/6 mice and 100 GLP1R/GIPR double-knockout mice. The transplantation experiment used 100 mice in five groups ($n = 20$/group); in vitro experiments were repeated at least three times, generally $n = 5$/group.	GLP1R single agonists and GLP1R/GIPR dual agonists; receptor knockdown/overexpression and knockout models.	Functional cell assays; RNA-seq, ChIP-seq, RIP-seq, immunoprecipitation; histology/lineage tracing; questionnaire-based periodontal assessment.	Data were expressed as mean ± SD and analyzed in GraphPad Prism 10.0. Two groups were compared with an unpaired two-tailed Student's *t*-test and multiple groups with one-way ANOVA. Chi-square analysis assessed the association between agonist use and periodontitis severity, and ordinal logistic regression assessed severity in relation to treatment duration; $p < 0.05$.	GLP1R agonism enhanced multilineage differentiation and periodontal regeneration and suppressed IFIT1/2/3-mediated translational inhibition. Treated survey participants had better periodontal staging/grading; observational results do not establish causality.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Liu Z, Zhou W, Tangl S, Liu S, Xu X, Rausch-Fan X. et al. [37]	2015	Potential mechanism of dental-implant osseointegration in a diabetic rat model.	Animal in vivo experiment.	Thirty-three Zucker diabetic fatty rats with two femoral implants each (66 implants), allocated to saline control, exenatide initiated at implantation, or exenatide administered until glycemia stabilized before implantation ($n = 11$/group). Animals were assessed at days 7 ($n = 4$/group), 14, 30, and 60 ($n = 6$/group at each time point).	Subcutaneous exenatide initiated at implantation or administered until serum glucose was stable (≤16 mmol/L), versus saline-treated diabetic controls.	Histology; TRAP-positive osteoclast counts; immunohistochemical localization and mean optical density of integrin α5β1 and fibronectin around implants.	Osteoclast counts and mean optical density were quantified with Image-Pro Plus 6.2. Between-group and within-group differences were assessed separately by one-way ANOVA after checking homogeneity with Levene's test; $p < 0.05$.	Exenatide combined with prior glycemic stabilization produced stronger peri-implant integrin α5β1 and fibronectin expression and altered osteoclast dynamics, supporting improved early osseointegration under controlled glycemia.
Chen, ZJ et al. [38]	2024	Exenatide versus insulin effects on T2D osteogenesis and implant osseointegration.	Mixed rat in vivo and rat-BMSC in vitro mechanistic study.	Forty male Sprague-Dawley rats entered T2DM induction. Twenty-one successfully modeled T2DM rats were randomized to PBS, insulin, or exenatide ($n = 7$/group); an additional seven non-diabetic rats served as controls. Rat BMSCs were used for mechanistic assays; experiments provided at least five independent values and technical triplicates where specified.	Exenatide versus insulin and PBS control.	Micro-CT, histology, dual fluorescent labeling, immunofluorescence/IHC, RT-PCR, and Western blotting.	Data were expressed as mean ± SD and analyzed in SPSS 26.0, GraphPad Prism 9, and OriginPro 8. Depending on design and assumptions, analyses used one-way or repeated-measures two-way ANOVA, Welch/Brown-Forsythe procedures, Tukey post hoc comparisons, or Kruskal–Wallis with Dunn's test; Geisser-Greenhouse correction was applied where appropriate; $p < 0.05$.	Exenatide produced greater peri-implant osteogenesis than insulin, activated LRP5/6/GSK-3β/β-catenin signaling, and modulated BMPR1A and β-TrCP pathways linked to adipogenesis and inflammation.
Zhang, YX et al. [39]	2020	Osteogenic, anti-inflammatory, and bone-protective effects of liraglutide in periodontitis.	Mixed hPDLC in vitro and rat in vivo experiment.	Human periodontal ligament cells used for in vitro experiments (≥3 independent experiments) and 32 male Wistar rats allocated to control ($n = 6$), liraglutide ($n = 6$), periodontitis plus saline ($n = 10$), or periodontitis plus liraglutide ($n = 10$).	Liraglutide versus Pg-LPS/periodontitis controls.	ALP/ARS, qRT-PCR, Western blotting, immunofluorescence, tissue inflammation, cytokines, and alveolar bone resorption.	Data were expressed as mean ± SD (figure-specific error bars also reported as SEM) and analyzed in SPSS 19.0 using one-way ANOVA; $p < 0.05$ (95% confidence level).	Liraglutide restored osteogenic markers and mineralization, modulated Wnt/β-catenin signaling, reduced TNF-α, IL-1β and IL-6, and limited inflammatory infiltration and alveolar bone loss.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Pang, YQ et al. [40]	2019	Liraglutide effects on hPDLC proliferation, migration, inflammation, and osteogenic differentiation.	In vitro experimental study.	Primary human periodontal ligament cells; the number of donors was not reported. Cells from the same donor were used within each experimental component, and each experiment was repeated at least three times (representative $n = 3$).	Liraglutide 25–125 nM with or without LPS; untreated/LPS controls.	qRT-PCR, MTT, wound healing, ELISA, ARS, and Western blotting.	Data were expressed as mean ± SD. Differences were tested using independent two-tailed *t*-tests; qRT-PCR and Western blot data were expressed as fold change relative to control; $p < 0.05$.	Liraglutide enhanced proliferation and migration, suppressed LPS-induced IL-6/TNF-α, and restored mineralization, ALP, and Runx2; 100 nM was reported as optimal.
Zhang, Z et al. [41]	2026	Semaglutide protection against osteoblast ferroptosis in diabetic periodontitis.	Mixed osteoblast in vitro and diabetic-mouse in vivo mechanistic study.	The animal experiment included five groups ($n = 6$/group): non-diabetic control, T2DM, diabetic periodontitis, diabetic periodontitis plus semaglutide, and diabetic periodontitis plus ferrostatin-1.	Semaglutide; Wnt5a siRNA and p38 agonist mechanistic controls.	EdU, Transwell, ALP/ARS, qPCR, Western blotting, ROS/Fe^{2+}/lipid-peroxidation assays, H&E, IHC, and immunofluorescence.	Data were expressed as mean ± SD and analyzed in GraphPad Prism 10. Two-group comparisons used Student's *t*-test; multiple groups used one-way ANOVA followed by Tukey's post hoc test; $p < 0.05$.	Semaglutide reduced oxidative stress and ferroptosis, restored osteogenic functions, and reduced periodontal inflammation through inhibition of Wnt5a/Ror2/p38 MAPK signaling.
Liu H. et al. [13]	2019	Exendin-4 regulation of inflammatory and osteogenic signaling in LPS-stimulated PDLSCs.	In vitro experimental mechanistic study.	Primary human periodontal ligament stem cells isolated from premolars extracted for orthodontic indications; donor count was not reported. Experiments were conducted on at least three independent occasions.	Exendin-4 with LPS stimulation versus relevant controls.	CCK-8, ARS, Western blotting, RT-PCR, ELISA, and immunofluorescence.	Analyses were performed in GraphPad Prism 7.0. Student's *t*-test was used for two-group comparisons and one-way ANOVA for multiple-group comparisons; $p < 0.05$.	Exendin-4 promoted osteogenic differentiation, increased Runx2/ALP/Osx, decreased TNF-α/IL-6, and modulated Wnt and NF-κB signaling.
Jiang T. et al. [42]	2026	Adjunctive metabolic support for periodontal regeneration in semaglutide-treated obesity-associated periodontitis.	Mixed biomaterial/cell in vitro and animal in vivo study.	Male C57BL/6J mice with diet-induced obesity and ligature-induced periodontitis, with five experimental groups ($n = 5$/group), plus primary BMSCs from obese mice and RAW264.7 cells. RNA sequencing used $n = 3$ biological replicates/group; other experiments included at least three biological replicates.	Systemic semaglutide with local metformin-loaded mesoporous polydopamine hydrogel (Met@MPDA-Gel), compared with study-specific controls.	Material characterization, cellular energy-metabolism/osteogenesis assays, and periodontal tissue/bone analyses.	Data were expressed as mean ± SEM and analyzed in GraphPad Prism 9 using Student's *t*-test, one-way ANOVA, or three-way ANOVA followed by Tukey's multiple-comparison test, as appropriate; $p < 0.05$.	Semaglutide partially attenuated inflammation-associated alveolar bone loss but did not restore osteogenic capacity adequately. Adjunctive Met@MPDA-Gel improved BMSC energy metabolism and promoted alveolar bone regeneration in the experimental model.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Zhai S, Liu C, Vimalraj S, Subramanian R, Abullais SS, Arora S, Saravanan S. et al. [17]	2023	GLP-1 receptor signaling in osteoblastic differentiation of dental pulp stem cells.	Mixed DPSC in vitro and zebrafish-scale ex vivo/in vivo study.	Human dental pulp stem cells and a zebrafish scale-regeneration model. Donor/fish numbers were not reported; experiments were based on at least three replicates.	Liraglutide treatment in human dental pulp stem-cell osteogenic differentiation experiments and a zebrafish scale-regeneration model, with corresponding control conditions and mechanistic assessment of the LINC00968/miR-3658/Runx2 pathway.	Osteogenic differentiation and mineralization assays with gene/protein analyses and zebrafish-scale regeneration assessment.	Data were expressed as mean ± SD from at least three replicates. One-way ANOVA was used, with Student's *t*-test for specified between-group comparisons; $p < 0.05$.	GLP-1R activation promoted osteoblastic differentiation and mineralized-tissue regeneration;
Liang Q. et al. [43]	2021	Combined SDF-1 and exendin-4 effects on PDLSCs and periodontal bone regeneration.	Mixed hPDLSC in vitro and animal periodontal-defect in vivo study.	Human periodontal ligament stem cells plus 60 male Wistar rats with bilateral periodontal fenestration defects. Rats were allocated to saline or exendin-4 systemic treatment ($n = 30$ each), with contralateral PBS- or SDF-1-loaded membranes; six rats from each arm were assessed at each of five time points. In vitro assays used triplicate or sextuplicate measurements, depending on outcome.	Exendin-4 with SDF-1 versus single-agent and control conditions.	Cell recruitment/proliferation and osteogenic assays; histologic and bone-regeneration assessment.	Data were expressed as mean ± SD and analyzed in GraphPad Prism 6. Differences among more than two groups were assessed by one- or two-way ANOVA followed by Tukey's honestly significant difference test; $p < 0.05$.	The combined intervention enhanced PDLSC-related regenerative responses and periodontal bone regeneration beyond control conditions.
Guo Z. et al. [16]	2018	Exendin-4 rescue of high-glucose-impaired osteogenic behavior in PDLSCs.	In vitro experimental study.	Human periodontal ligament stem cells isolated from healthy premolars of donors aged 18–25 years; donor count was not reported. Assays were repeated three times or performed in at least three independent experiments.	Exendin-4 under high-glucose conditions versus normo-glycemic/high-glucose controls.	Proliferation, migration, ALP/mineralization, and osteogenic gene/protein analyses.	Data were expressed as mean ± SD and analyzed in SPSS 22.0. Student's *t*-test compared two groups; one-way ANOVA compared ≥3 groups, followed by LSD (equal variances) or Dunnett's T3 (unequal variances). Kruskal–Wallis H was used for non-normal data; $p < 0.05$.	Exendin-4 counteracted high-glucose-associated impairment of PDLSC proliferation, migration, and osteogenic differentiation.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Shen W.-R. et al. [44]	2021	Effect of local high-dose exendin-4 on orthodontic tooth movement and bone remodeling.	Animal in vivo orthodontic experiment.	Sixteen 8-week-old male C57BL/6J mice undergoing orthodontic tooth movement, allocated to vehicle or local exendin-4 at 0.2, 4, or 20 μg ($n = 4$/group).	Local high-dose exendin-4 versus vehicle/control.	Tooth-movement measurement, histology, osteoclast/bone-remodeling assessments.	Data were expressed as mean ± SD and analyzed in SPSS using Student's *t*-test or ANOVA followed by Scheffé's post hoc test; $p < 0.05$.	Local high-dose exendin-4 inhibited orthodontic tooth movement, consistent with altered osteoclast activity and bone remodeling.
Moraes R.M. et al. [14]	2015	Effects of exenatide and sitagliptin on inflammatory mediators and tissue destruction in experimental periodontitis.	Animal in vivo experiment.	Forty male Wistar rats randomized to four groups ($n = 10$/group): control, ligature-induced periodontitis, periodontitis plus exenatide, or periodontitis plus sitagliptin. ELISA analyses used $n = 8$/group.	Exenatide or sitagliptin versus periodontitis control.	Inflammatory gene/protein markers, MMP-9, collagen degradation, and alveolar bone loss.	Sample size was calculated in G*Power (power 80%, $\alpha = 0.05$). Data were analyzed by ANOVA or Kruskal–Wallis according to distribution, followed by Tukey or Dunn post hoc tests when appropriate; $\alpha = 0.05$.	Both drugs reduced Il1b, Nos2, and Mmp9 expression, but did not stabilize or reduce alveolar bone loss or collagen degradation.
Oyewole S.O. et al. [45]	2026	Risk of orofacial adverse events among GLP-1RA users.	Multinational retrospective propensity-matched cohort study.	Multinational TriNetX cohort comprising 226,485 GLP-1RA users and an age- and sex-matched comparator cohort (1:1); outcome-specific denominators varied after exclusion of prevalent conditions.	GLP-1RA exposure versus 1:1 age- and sex-matched controls.	TriNetX electronic-health-record analysis using ICD-10 orofacial outcomes.	Propensity-score matching (1:1) was based on age and sex. Orofacial outcome prevalences were compared using odds ratios with 95% confidence intervals; $p < 0.05$.	Most orofacial outcomes were not increased and several showed inverse associations (OR 0.295–0.893). GERD was increased (5.36%; OR 1.329, 95% CI 1.291–1.367). Residual confounding remains possible.
Memida, T et al. [26]	2026	Relative effects of glycemic control and systemic inflammation on periodontal/peri-implant destruction, immunity, and microbiota.	Animal in vivo experiment with microbiome and ex vivo functional analyses.	Seventy-five male mice overall, including wild-type controls and db/db diabetic mice assigned to untreated, liraglutide, indomethacin, or combined-treatment conditions. At least eight successfully osseointegrated implants/group were obtained; endpoint-specific n ranged from 3–7/group, microbiome $n = 4$–6/group, and in vitro assays $n = 6$.	Liraglutide, indomethacin, combined treatment, and ligation/control conditions.	Bone loss, cytokines, osteoclasts, RAGE, IL-17/Treg profiling, metagenomics, and in vitro cytokine induction by microbiota.	Data were generally expressed as mean ± SEM and analyzed in GraphPad Prism 10 using one-way ANOVA followed by Dunnett's test (multiple treatments vs. one control) or Tukey's test (all pairwise comparisons); $p < 0.05$. Microbiome β-diversity differences were assessed by PERMANOVA.	Liraglutide reduced bone loss and immune dysregulation, restored Foxp3+ Tregs, and shifted oral microbiota toward normoglycemic controls; peri-implant communities were more intervention-resistant.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Li, RX et al. [18]	2026	Liraglutide regulation of DPSC proliferation and osteogenesis through histone lactylation.	In vitro mechanistic study.	Human dental pulp stem cells studied in vitro; donor/source sample size was not reported. Experiments were independently repeated at least three times.	Liraglutide with oxamate/Nala modulation and DSPP rescue experiments.	CCK-8, EdU, ALP, ARS, Western blotting, ChIP, dual-luciferase, and RT-qPCR.	Data were expressed as mean ± SD and analyzed in GraphPad Prism 8. Student's *t*-test was used for two-group comparisons and one-way ANOVA for multiple groups; $p < 0.05$.	Liraglutide enhanced proliferation and osteogenesis by increasing H3K18 lactylation and DSPP transcription; pharmacologic modulation and DSPP rescue supported the proposed pathway.
Pang, YQ et al. [46]	2025	Topical sustained liraglutide delivery for diabetic periodontitis through necroptosis inhibition.	Mixed biomaterial/in vitro cytocompatibility and diabetic-rat in vivo study.	Human periodontal ligament cells plus 60 male Wistar rats initially enrolled. Twelve non-diabetic rats formed control and periodontitis groups ($n = 6$ each); after nine diabetes-related deaths, 39 diabetic rats were allocated to diabetes control ($n = 7$) and four diabetic-periodontitis treatment/comparator groups ($n = 8$ each).	LIRA@PLGA/HA for 4 weeks versus controls and PERIOCLINE® comparator.	Nanoparticle characterization/release, CCK-8, histology, ELISA, micro-CT, qRT-PCR, and Western blotting.	Data were expressed as mean ± SD and analyzed in SPSS using one-way ANOVA; $p < 0.05$.	The system achieved 86.2% encapsulation, 4.3% loading and ~60% release by day 8; it reduced TNF-α/IL-1β, inflammation, bone resorption, and RIPK1/RIPK3/MLKL expression, with effects similar to PERIOCLINE®.
Li, JM et al. [25]	2026	Localized liraglutide delivery by injectable hydrogel for diabetic periodontitis.	Mixed biomaterial/cell in vitro and diabetic-rat in vivo study.	Human periodontal ligament cells, P. gingivalis cultures, and 25 male Wistar rats with diabetic periodontitis allocated to five groups ($n = 5$/group). In vitro experiments were generally repeated three times ($n = 3$).	LIRA@CMCS-OD hydrogel versus relevant unloaded/control conditions.	Material/drug-release characterization, antibacterial and ROS assays, hPDLC osteogenesis, periodontal inflammation, tooth mobility, bone regeneration, and biosafety.	Data were expressed as mean ± SD and analyzed in GraphPad Prism 9 and OriginPro 2021. Two groups were compared using a two-tailed Student's *t*-test and multiple groups using one-way ANOVA; $p < 0.05$.	The hydrogel inhibited P. gingivalis, reduced intracellular ROS, promoted hPDLC osteogenesis, and improved gingival inflammation, tooth mobility, and alveolar bone regeneration.

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Jung J.-E. et al. [24]	2026	Exendin-4 effects on aging-model hyposalivation and salivary-gland injury.	Animal in vivo experiment.	Forty male Sprague-Dawley rats; four groups ($n = 10$/group).	D-galactose 300 mg/kg/day for 7 weeks, followed by exendin-4 0.5 or 1 μg/head for 2 weeks.	Salivary flow, histology, biochemical analyses, mucin histochemistry, and TUNEL apoptosis assay.	Mean ± SEM; one-way ANOVA with Tukey's test; $p < 0.05$.	Exendin-4 improved salivary secretion, preserved acinar morphology, reduced acidic/neutral mucin accumulation, and decreased salivary-gland apoptosis.
Li, FT et al. [47]	2023	Liraglutide protection against periodontal inflammation, oxidative stress, and bone loss via Nrf2/HO-1.	Animal in vivo mechanistic experiment.	Wistar rats with ligature-induced periodontitis treated with different liraglutide doses and, in mechanistic experiments, adenoviral si-Nrf2 or si-NC;	Multiple liraglutide doses; saline controls; adenoviral si-Nrf2 versus si-NC.	Micro-CT, H&E/IHC, TRAP, ELISA, RT-qPCR, and Western blotting.	The study reports a significance threshold of $p < 0.05$ but does not identify the statistical tests used.	Liraglutide dose-dependently reduced osteoclasts, MDA, TNF-α, IL-1β and IL-6 and increased GSH-Px/Nrf2/HO-1/NQO1; Nrf2 knockdown reversed these effects.
Shi, SJ et al. [20]	2021	Peri-implant marginal bone loss and clinical parameters under different glucose-lowering medications.	Retrospective clinical cohort study.	At 1 year: 150 patients with 308 implants (insulin: 54/101; metformin: 54/121; GLP-1 drugs: 42/86). At 2 years: 71 patients with 129 implants according to the Results section and group-level counts (insulin: 30/53; metformin: 24/44; GLP-1 drugs: 17/32). The implant was the unit of analysis.	GLP-1 drugs versus insulin versus metformin monotherapy.	Periapical radiographic marginal bone level; probing depth and bleeding on probing.	Sample size was estimated in PASS (80% power, $\alpha = 0.05$; ≥43 implants/group). Analyses used SPSS 25: chi-square/ANOVA for baseline comparisons, Shapiro–Wilk normality testing, Kruskal–Wallis with Bonferroni-adjusted post hoc comparisons, and ANCOVA with Bonferroni correction for covariate adjustment; $p < 0.05$.	Marginal bone loss was lower with GLP-1 drugs than with insulin or metformin at 1 year ($p < 0.01$) and lower than metformin at 2 years ($p < 0.01$); probing depth and bleeding did not differ ($p > 0.05$).

Table 1. *Cont.*

Author	Year	Focus of Investigation	Type of Study	Sample/Model and Size	GLP-1RA Intervention/Exposure and Comparator	Type of Analysis/Outcomes	Statistical Analysis	Key Results
Zhou, WJ et al. [48]	2015	Glycemic-control timing/exenatide microspheres and serum bone-turnover markers after implantation.	Animal in vivo implant experiment.	Thirty-three Zucker diabetic fatty rats with 66 implants, allocated to three groups ($n = 11$/group).	The intervention was reported inconsistently: the title and conclusion refer to delayed-release exenatide microspheres, whereas the methods description refers to insulin-based treatment groups.	Serum bone Gla protein and alkaline phosphatase by ELISA at days 7, 14, and 30.	SPSS 17.0 was used and $p < 0.05$ defined statistical significance;	ALP was higher in treated/glycemically controlled groups; BGP changes were time-dependent and considered poorly related to local osseointegration.

For Mawardi et al., the source reports modified Schirmer measurements in mL, although strip wetting is conventionally expressed in mm. The intended unit could not be verified; no conversion was made, and these values are not interpreted as salivary volume or flow rate [22,49].

3.3. Bibliometric Analysis

The exploratory bibliometric analysis of the 27 included publications characterized the thematic structure, geographical distribution, international collaboration, and temporal development of the literature. The author-keyword co-occurrence network is presented in Figure 2, while country-level co-authorship patterns and their distribution by average publication year are shown in Figure 3.

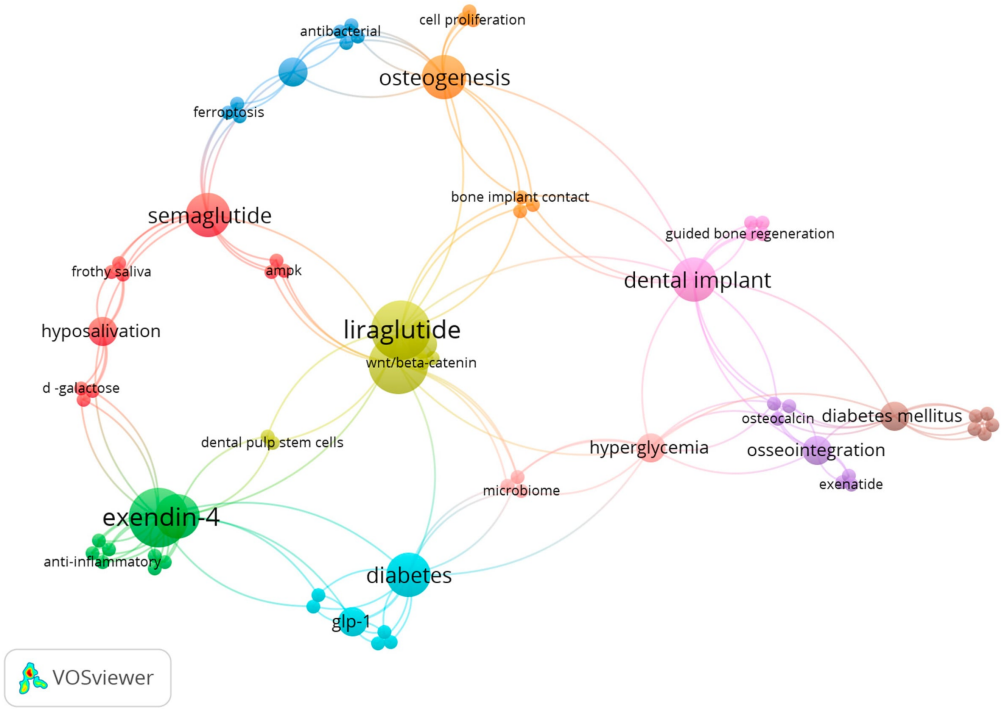


Figure 2. Keyword Co-Occurrence Network of GLP-1 Receptor Agonist Research in Periodontal and Oral Health.

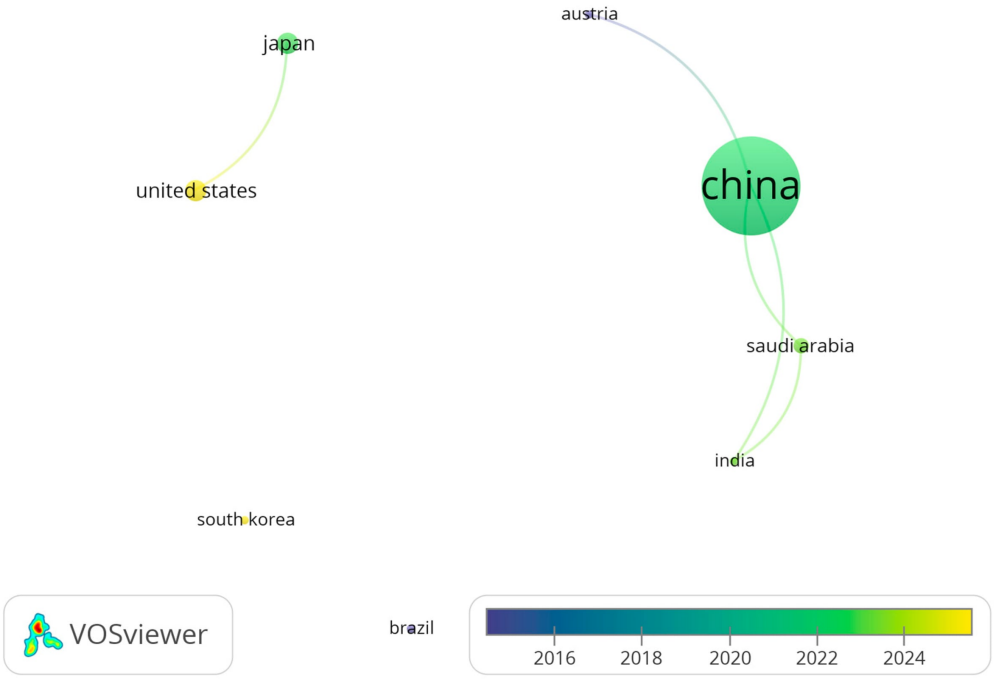


Figure 3. Country-Level Co-Authorship and Temporal Distribution.

3.3.1. Keyword Co-Occurrence Analysis

Author-keyword co-occurrence analysis was conducted using a minimum occurrence threshold of one to preserve the terminological breadth of the comparatively small evidence base. The resulting network displayed an interconnected multicluster structure linking agent-specific terminology with metabolic, inflammatory, osteogenic, salivary, and implant-related concepts (Figure 2).

Liraglutide formed one of the most prominent and centrally positioned nodes, with visible connections to osteogenesis, Wnt/β-catenin signaling, dental pulp stem cells, diabetes, and bone–implant contact. Exendin-4 and semaglutide also formed prominent but spatially distinct nodes, whereas exenatide appeared as a smaller node within the implant- and osseointegration-related region. Semaglutide was positioned near terms related to hyposalivation, frothy saliva, AMPK signaling, and ferroptosis, while exendin-4 was associated with anti-inflammatory and diabetes-related terminology. Osteogenesis represented another prominent theme and was connected to terms describing cell proliferation, antibacterial activity, ferroptosis, and bone–implant contact.

The implant-related portion of the network included dental implant, osseointegration, hyperglycemia, diabetes mellitus, guided bone regeneration, osteocalcin, and bone–implant contact. Microbiome appeared as a comparatively small node positioned between the metabolic, periodontal, and implant-related regions. Diabetes and GLP-1 occupied an intermediary position linking several compound-specific and oral-health domains.

The separate representation of liraglutide, semaglutide, exenatide, and exendin-4 indicates that the included publications commonly used individual compound names rather than a consistent GLP-1RA class descriptor. Overall, the network depicts an interconnected but pharmacologically and methodologically heterogeneous literature organized around specific agonists and their experimental or oral-health applications. Node size and connectivity represent keyword occurrence and co-occurrence within the analyzed corpus and should not be interpreted as evidence of comparative efficacy, biological causality, temporal progression, or methodological quality.

3.3.2. Geographical Distribution and International Collaboration

The country-level co-authorship analysis identified contributions from eight countries distributed across four clusters and connected by five international co-authorship links (Figure 3). China formed the largest node, indicating the highest publication count within the analyzed corpus. Austria, Brazil, India, Japan, Saudi Arabia, South Korea, and the United States were represented by smaller publication outputs.

The largest connected component comprised China, Austria, India, and Saudi Arabia. China was linked to each of the other three countries, and an additional collaboration was identified between India and Saudi Arabia. A separate bilateral link connected the United States and Japan. Brazil and South Korea appeared as isolated nodes, indicating that their contributions did not involve international co-authorship with other countries represented in the corpus. Overall, international collaboration was limited to a small number of partnerships, while most research activity remained nationally concentrated.

The overlay visualization indicated variation in the average publication year of national contributions. Austria was positioned toward the earlier end of the temporal scale, whereas the United States and South Korea were associated with more recent average publication years. China occupied an intermediate position. Because several countries contributed only a small number of publications, their average publication years may be strongly influenced by individual studies and should therefore be interpreted descriptively rather than as evidence of stable temporal trends.

3.4. Risk of Bias Assessment

Methodological appraisal was performed at the level of the eligible evidence component. The 27 included publications generated 38 component-level assessments: five human, 19 animal in vivo, and 14 in vitro components. Mixed-design publications were therefore represented in more than one appraisal when appropriate. Human evidence was assessed with design-specific JBI checklists, animal evidence with SYRCLE, and in vitro evidence with QUIN (Tables 2–4). Judgments were based on information reported in the source publications; insufficient reporting was classified as unclear or not reported rather than being treated as evidence that a methodological safeguard had not been implemented. No cross-design summary score was calculated.

The five human components comprised a retrospective implant cohort [20], a retrospective matched electronic-health-record cohort [45], a pharmacovigilance analysis [23], a three-patient case series [22], and the questionnaire-based observational component of the mixed-design study by Shen et al. [36] (Table 2).

The implant cohort described exposure groups, outcomes, and statistical analyses comparatively well, but attrition between the one- and two-year assessments and the use of implants rather than patients as the analytical unit remained important limitations. In the multinational electronic-health-record cohort, matching was restricted to age and sex; residual confounding, outcome ascertainment, and completeness of follow-up therefore remained concerns. Neither cohort provided sufficient information to conclude that incomplete observations were handled without risk of bias. JBI results were reported item by item because the checklists do not support a validated universal numerical score across designs.

The pharmacovigilance and survey components identified their data sources, populations, comparisons, and analytical approaches, but exposure or outcome measurement and control of confounding were incompletely documented. The FAERS analysis was therefore interpreted as evidence of disproportionate reporting rather than incidence or causality. The three-patient case series reported clinical presentation, assessment, management, and follow-up, but did not establish consecutive or complete case inclusion. Its descriptive analysis was considered appropriate for the design. These limitations informed interpretation but were not used to exclude human studies.

Nineteen animal in vivo components were assessed using SYRCLE (Table 3). Baseline characteristics were judged at low risk in 16 components and unclear in three. For incomplete outcome data, nine components were judged at low risk, eight at unclear risk, and two at high risk. The high-risk judgments reflected conditioning analyses on successful osseointegration or substantial mortality followed by changes in group composition. The "other bias" domain was judged at low risk in five components, unclear in twelve, and high in two. High risk in this domain was assigned only when a specific concern was documented, including post-induction reallocation after mortality or internally inconsistent reporting of the intervention; incomplete reporting alone resulted in an unclear judgment.

Sequence generation, allocation concealment, random housing, blinding of caregivers or investigators, random selection for outcome assessment, blinding of outcome assessors, and selective outcome reporting were generally insufficiently described. These domains were therefore judged unclear unless the publication provided explicit information supporting another judgment. No overall SYRCLE category was assigned because the tool is domain-based and does not prescribe a validated algorithm for collapsing heterogeneous domain judgments into a single rating. Accordingly, high-risk judgments in individual domains are presented directly rather than being obscured by a global label.

Table 2. JBI Critical Appraisal of the Human Evidence Components. (**A**) Cohort studies. (**B**) Pharmacovigilance and cross-sectional survey components. (**C**) Case series.

(**A**)

Study	DOI	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Key Limitation
Oyewole S.O. et al. (2026)	10.1016/j.oooo.2026.06.002	U	Y	U	N	N	Y	U	U	U	N	Y	Matching was limited to age and sex; exposure/outcome coding and follow-up completeness were insufficiently documented.
Shi S.J. et al. (2021)	10.1186/s12903-021-01583-3	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Substantial loss between the 1- and 2-year analyses; implant-level analysis included multiple implants from some participants.

(**B**)

Study	DOI	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Key Limitation
Khan F.I. et al. (2025)	10.1002/lary.32061	Y	Y	U	Y	N	N	U	Y	FAERS disproportionality analysis detects reporting signals but lacks exposure denominators, does not adequately control for confounding, and does not permit clinical validation of individual reports.
Shen Y.F. et al. (2026)	10.1186/s11658-026-00867-2	Y	Y	U	Y	N	N	U	Y	The human survey was cross-sectional; medication exposure, oral outcomes, and confounder control were not described with sufficient detail for causal interpretation.

(**C**)

Study	DOI	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Key Limitation
Mawardi H.H. et al. (2023)	10.1097/MD.0000000000036730	U	Y	Y	U	U	Y	Y	Y	Y	Y	Only three cases; consecutive and complete inclusion was not demonstrated, and alternative explanations cannot be excluded by the uncontrolled design.

Assessments are reported at the component level. The 27 included publications contributed 38 assessments across Tables 2–4. Mixed-design publications were counted once in the evidence corpus, while their eligible components were assessed separately using the corresponding design-specific instruments. Abbreviations: Y, yes; N, no; U, unclear; NA, not applicable. JBI does not prescribe a universal numerical score across different checklist designs. Cohort Q1–Q11 and cross-sectional Q1–Q8 correspond to the design-specific JBI items; case-series Q1–Q10 correspond to the JBI case-series checklist. The pharmacovigilance and survey components in Panel (**B**) were appraised using the JBI analytical cross-sectional checklist.

Table 3. SYRCLE Risk-of-Bias Assessment of the Animal In Vivo Components.

Study	DOI	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Principal Basis for Judgment
Yang M. et al. (2022)	10.1155/2022/8260111	U	L	U	U	U	U	U	L	U	L	Randomized designation and balanced groups were reported; sequence method, concealment, housing, and blinding were not explicit.
Sawada N. et al. (2020)	10.1155/2020/8843310	U	L	U	U	U	U	U	U	U	L	Randomization and sample-size estimation were reported, but key allocation and blinding safeguards were not described. Outcome-specific denominators were not fully accounted for, so incomplete outcome data were judged unclear.
Wang Y. et al. (2024)	10.1111/odi.14931	U	L	U	U	U	U	U	L	U	U	Four small rat groups were described; random sequence, concealment, housing, and blinded assessment were not documented.
Shen Y.F. et al. (2026)	10.1186/s11658-026-00867-2	U	L	U	U	U	U	U	U	U	U	Large experimental programme with reported group sizes; allocation and blinding procedures remained insufficiently reported.
Liu Z. et al. (2015)	10.1016/j.bjoms.2015.05.023	U	L	U	U	U	U	U	U	U	U	Group and time-point numbers were reported; randomization and blinded histological assessment were not established.
Chen Z.J. et al. (2024)	10.1111/bph.16421	U	L	U	U	U	U	U	L	U	U	Model induction losses were reported before group allocation; random sequence and blinding details were incomplete.
Zhang Y.X. et al. (2020)	10.1016/j.jdent.2020.103310	U	L	U	U	U	U	U	L	U	U	Group sizes and outcomes were reported, but allocation, housing, and assessor blinding were not explicit.
Zhang Z. et al. (2026)	10.2147/DDDT.S599539	U	L	U	U	U	U	L	L	U	L	Random allocation was reported, but the sequence-generation method was not specified. Histological evaluation and immunohistochemical quantification were performed by investigators blinded to group allocation.
Jiang T. et al. (2026)	10.1016/j.mtbio.2026.103231	U	L	U	U	U	U	U	U	U	U	Group sizes were reported, but endpoint-specific subsampling and most bias-control procedures were incompletely described.
Zhai S. et al. (2023)	10.1016/j.peptides.2023.170974	U	U	U	U	U	U	U	U	U	U	The publication did not report the number of animals or the allocation procedures used for the zebrafish-scale component.
Liang Q. et al. (2021)	10.1111/cpr.12997	U	L	U	U	U	U	U	L	U	L	Animal allocation and endpoint numbers were reported; random sequence, concealment, and blinding were not explicit.

Table 3. *Cont.*

Study	DOI	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Principal Basis for Judgment
Shen W.-R. et al. (2021)	10.2319/021320-103.1	U	L	U	U	U	U	U	L	U	U	Equal groups were reported, but the very small sample and unreported allocation/blinding methods limit confidence.
Moraes R.M. et al. (2015)	10.1902/jop.2015.150278	U	L	U	U	U	U	U	U	U	L	Randomization and a priori power calculation were reported; sequence method, concealment, and blinding were not explicit. Outcome-specific denominators were not fully accounted for, so incomplete outcome data were judged unclear.
Memida T. et al. (2026)	10.3389/fimmu.2026.1847456	U	L	U	U	U	U	U	H	U	U	Endpoint-specific samples varied, and implant analyses required successful osseointegration, creating a specific risk of attrition-related selection.
Pang Y.Q. et al. (2025)	10.1016/j.mtbio.2025.101582	U	L	U	U	U	U	U	H	U	H	Nine diabetes-related deaths and post-induction reallocation produced unequal groups; allocation and blinding safeguards were not reported.
Li J.M. et al. (2026)	10.1016/j.jconrel.2026.114688	U	L	U	U	U	U	U	L	U	U	Equal groups and multiple controls were reported; random sequence, concealment, and blinding remained unclear.
Jung J.-E. et al. (2026)	10.1016/j.ejphar.2025.178445	U	U	U	U	U	U	U	U	U	U	Group sizes and statistical methods were reported; however, random sequence generation, allocation concealment, random housing, and blinding procedures were not described.
Li F.T. et al. (2023)	10.23812/j.biol.regul.homeost.agents.20233702.102	U	U	U	U	U	U	U	U	U	U	Sample sizes and statistical tests were not reported; consequently, the relevant bias-control procedures could not be assessed.
Zhou W.J. et al. (2015)	10.1111/cid.12184	U	L	U	U	U	U	U	L	U	H	Group sizes were reported; however, the intervention was described inconsistently, with the title and conclusion referring to exenatide microspheres and the methods description referring to insulin-based treatment groups.

Assessments are reported at the component level. The 27 included publications contributed 38 assessments across Tables 2–4. Mixed-design publications were counted once in the evidence corpus, while their eligible components were assessed separately using the corresponding design-specific instruments. Abbreviations: L, low risk; H, high risk; U, unclear risk. D1, sequence generation; D2, baseline characteristics; D3, allocation concealment; D4, random housing; D5, blinding of caregivers/investigators; D6, random outcome assessment; D7, blinding of outcome assessor; D8, incomplete outcome data; D9, selective outcome reporting; D10, other bias. Domain judgments reflect the information reported in each publication; U indicates insufficient information and should not be interpreted as proof that the safeguard was absent.

Table 4. QUIN Methodological Appraisal of the In Vitro Components.

Study	DOI	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Score (%)	Risk
Wang Y. et al. (2024)	10.1111/odi.14931	2	0	2	2	2	0	0	2	0	0	2	2	58.3	Moderate
Shen Y.F. et al. (2026)	10.1186/s11658-026-00867-2	2	0	2	2	2	0	0	2	0	0	2	2	58.3	Moderate
Chen Z.J. et al. (2024)	10.1111/bph.16421	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Zhang Y.X. et al. (2020)	10.1016/j.jdent.2020.103310	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Pang Y.Q. et al. (2019)	10.1111/jre.12607	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Zhang Z. et al. (2026)	10.2147/DDDT.S599539	2	0	2	2	2	0	0	2	0	0	2	2	58.3	Moderate
Liu H. et al. (2019)	10.1016/j.intimp.2019.105801	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Jiang T. et al. (2026)	10.1016/j.mtbio.2026.103231	2	0	2	2	2	0	0	2	0	0	2	2	58.3	Moderate
Zhai S. et al. (2023)	10.1016/j.peptides.2023.170974	2	0	1	2	1	0	0	2	0	0	2	2	50.0	Moderate
Liang Q. et al. (2021)	10.1111/cpr.12997	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Guo Z. et al. (2018)	10.1016/j.archoralbio.2018.03.014	2	0	2	2	2	0	0	2	0	0	2	2	58.3	Moderate
Li R.X. et al. (2026)	10.1007/s13770-026-00801-9	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Pang Y.Q. et al. (2025)	10.1016/j.mtbio.2025.101582	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate
Li J.M. et al. (2026)	10.1016/j.jconrel.2026.114688	2	0	1	2	2	0	0	2	0	0	2	2	54.2	Moderate

Assessments apply only to the eligible in vitro component of each publication. Mixed-design publications were counted once in the evidence corpus, while their eligible components were appraised separately. Randomization or blinding reported for an animal component was not transferred to the in vitro assessment. Scores: 2, adequately specified; 1, inadequately specified; 0, not specified. A score of 0 indicates insufficient reporting in the assessed source, rather than confirmation that the procedure was not performed. Percentage score = obtained score / maximum applicable score × 100. Risk categories: low, >70%; moderate, 50–70%; high, <50%. Q1, aims/objectives; Q2, sample-size calculation; Q3, sampling technique; Q4, comparison group; Q5, methodology details; Q6, operator details; Q7, randomization; Q8, outcome-assessment method; Q9, outcome-assessor details; Q10, blinding; Q11, statistical analysis; Q12, results presentation.

The 14 in vitro components were evaluated using QUIN (Table 4). Aims, comparison groups, outcome-assessment methods, statistical analyses, and results were generally reported. None of the components documented a formal sample-size calculation or adequate blinding, and reporting of sampling procedures, operator characteristics, random allocation, and outcome-assessor characteristics was limited. After criterion-level reassessment, QUIN scores ranged from 50.0% to 58.3%; all 14 components were classified as having a moderate risk of bias. These ratings primarily reflect incomplete reporting of design safeguards rather than evidence that the experimental findings were invalid.

Across evidence streams, the principal limitations were residual confounding and incomplete follow-up in human observational studies, insufficient reporting of allocation and blinding procedures in animal experiments, and insufficient reporting of sample-size justification and blinding in in vitro studies. The appraisal did not support a single hierarchy or pooled quality estimate because JBI, SYRCLE, and QUIN address different constructs. Its purpose was to qualify the certainty and translational relevance of each evidence stream, not to exclude studies or convert methodological reporting into an estimate of treatment effect.

3.5. Periodontal Inflammation, Immune Regulation, and Alveolar Bone Loss

A substantial proportion of the preclinical evidence investigated the effects of GLP-1 receptor activation on periodontal inflammation and alveolar bone destruction. Across ligature-induced, bacterial lipopolysaccharide-stimulated, diabetic, and obesity-associated models, liraglutide, semaglutide, exenatide, and exendin-4 were generally associated with lower expression or concentrations of pro-inflammatory mediators. In a ligature-induced periodontitis model, Sawada et al. [12] reported that liraglutide reduced inflammatory-cell infiltration, macrophage accumulation, TNF-α and inducible nitric oxide synthase expression, M1 macrophage polarization, osteoclast numbers, and alveolar bone resorption. Similarly, Zhang et al. [39] found that liraglutide reduced periodontal inflammatory infiltration and the expression of TNF-α, IL-1β, and IL-6, while attenuating alveolar bone loss. In another rat investigation, liraglutide exerted dose-dependent antioxidant and anti-inflammatory effects associated with activation of the Nrf2/HO-1 pathway.

These effects included reduced malondialdehyde, TNF-α, IL-1β, IL-6, and osteoclast numbers, together with increased glutathione peroxidase, Nrf2, HO-1, and NQO1 expression. Experimental Nrf2 knockdown diminished these responses. Exenatide and exendin-4 also modified inflammatory pathways in periodontal models. Moraes et al. [14] found that exenatide reduced Il1b, Nos2, and Mmp9 expression in ligature-induced periodontitis. However, these molecular changes were not accompanied by a significant reduction in alveolar bone loss or collagen degradation. In LPS-stimulated periodontal ligament stem cells, exendin-4 reduced TNF-α and IL-6 expression and modulated NF-κB- and Wnt-related signaling. Liraglutide similarly suppressed LPS-induced IL-6 and TNF-α expression in human periodontal ligament cells. Recent investigations expanded the proposed mechanisms beyond conventional cytokine suppression. Semaglutide reduced oxidative stress, lipid peroxidation, iron accumulation, and osteoblast ferroptosis in diabetic periodontitis through modulation of the Wnt5a/Ror2/p38 MAPK pathway. A locally delivered liraglutide formulation reduced the expression of RIPK1, RIPK3, and MLKL in diabetic periodontal tissues, consistent with inhibition of necroptosis. Another liraglutide-containing hydrogel reduced intracellular reactive oxygen species and local periodontal inflammation in addition to improving clinical and bone-related outcomes in diabetic rats. Immune-cell regulation was assessed in a diabetic periodontal and peri-implant model by Memida et al. [26] who reported that liraglutide reduced local bone loss and immune dysregulation and restored Foxp3-positive regulatory T-cell responses. The study also compared the effects of glycemic control through liraglutide with those of systemic inflammatory

suppression through indomethacin, alone and in combination. Collectively, the periodontal studies showed a predominantly favorable direction of effect for inflammatory, oxidative-stress, immune, and osteoclast-related outcomes. Nevertheless, improvements in molecular inflammatory markers were not uniformly accompanied by measurable preservation of periodontal hard tissues.

3.6. Osteogenic Differentiation and Periodontal Regeneration

Multiple in vitro and mixed-design studies [25,46] examined the influence of GLP-1 receptor activation on osteogenic differentiation, mineralization, and periodontal regenerative capacity. The cellular models included human periodontal ligament cells, periodontal ligament stem cells, dental pulp stem cells, human and rat bone-marrow stromal cells, and MC3T3-E1 osteoblast-lineage cells. Liraglutide increased alkaline phosphatase activity, mineralized nodule formation, and the expression of osteogenic markers in periodontal ligament cells and bone-marrow stromal cells. The reported signaling pathways included BMP2/Smad/Runx2 and Wnt/β-catenin. In human alveolar bone-marrow stromal cells obtained from participants with and without type 2 diabetes, liraglutide produced a concentration-dependent osteogenic response. A concentration of 10^{-8} mol/L was reported as optimal, whereas concentrations above 10^{-7} mol/L adversely affected the assessed cellular responses. Liraglutide also enhanced dental pulp stem-cell proliferation and osteogenic differentiation through increased H3K18 lactylation and DSPP transcription. Pharmacological modulation and DSPP rescue experiments supported the involvement of this pathway.

Zhai et al. reported that GLP-1 receptor activation promoted osteogenic differentiation of dental pulp stem cells and mineralized-tissue regeneration in a zebrafish scale model [17]. Exendin-4 enhanced periodontal ligament stem-cell proliferation, migration, alkaline phosphatase activity, mineralization, and the expression of Runx2, osterix, and other osteogenic markers. Under high-glucose conditions, exendin-4 counteracted the impairment of periodontal ligament stem-cell proliferation, migration, and osteogenic differentiation. When combined with stromal cell-derived factor 1, exendin-4 enhanced cell recruitment and periodontal bone regeneration in an experimental periodontal-defect model. The regenerative effects of receptor signaling were further examined by Shen et al. [36] who reported that GLP1R/GIPR signaling contributed to periodontal ligament stem-cell maintenance and multilineage differentiation, while receptor loss impaired regenerative responses. Agonist exposure suppressed IFIT1/2/3-mediated translational inhibition and enhanced periodontal tissue regeneration in the experimental models. Local drug-delivery approaches were evaluated in several recent studies. Liraglutide-loaded PLGA/hydroxyapatite particles and an injectable liraglutide-containing hydrogel improved osteogenic responses and periodontal bone formation in diabetic models. Jiang et al. evaluated systemic semaglutide with locally delivered Met@MPDA-Gel, a metformin-loaded material. Regenerative improvements observed with the combined intervention cannot be attributed to semaglutide alone [42]. Osteogenic and regenerative responses were reported in several experimental settings, but were not uniform and depended on the investigated agent, dose, metabolic context, delivery system, and model.

3.7. Peri-Implant Bone Formation and Osseointegration

Evidence regarding peri-implant outcomes was derived from animal experiments, mixed cellular–animal studies, one retrospective clinical cohort, and one investigation combining periodontal, peri-implant, immune, and microbiome analyses. In diabetic rat models, exenatide improved biological markers associated with early osseointegration. Liu et al. [37] found that exenatide administered after prior glycemic stabilization increased peri-implant integrin α5β1 and fibronectin expression and altered osteoclast dynamics. Chen

et al. [38] subsequently reported that exenatide produced greater peri-implant osteogenesis than insulin in a type 2 diabetes model. These responses were associated with activation of LRP5/6/GSK-3β/β-catenin signaling and modulation of BMPR1A- and β-TrCP-related pathways. Liraglutide enhanced peri-implant bone formation and integration in both non-diabetic Wistar rats and Goto-Kakizaki rats. The accompanying in vitro experiments showed enhanced osteogenesis of human alveolar bone-marrow stromal cells, including cells obtained from participants with type 2 diabetes.

The available clinical evidence was limited to a retrospective cohort comparing implants placed in patients receiving insulin, metformin, or GLP-1 receptor agonist monotherapy. Marginal bone loss was lower in the GLP-1 receptor agonist group than in the insulin and metformin groups at one year and lower than in the metformin group at two years. No significant differences were observed in probing depth or bleeding on probing. The analysis used the implant as its unit, with multiple implants contributed by some participants.

In the diabetic mouse model evaluated by Memida et al. [26], liraglutide reduced peri-implant bone destruction and immune dysregulation. However, peri-implant microbial communities appeared less responsive to metabolic and anti-inflammatory interventions than periodontal communities.

Overall, the peri-implant findings favored improved bone formation or reduced marginal bone loss during GLP-1 receptor agonist exposure. Nevertheless, the clinical evidence was derived from a single retrospective cohort, while most mechanistic findings originated from small animal studies.

3.8. Salivary Function, Xerostomia, and Salivary-Gland Outcomes

The evidence concerning salivary outcomes was limited and showed different directions of effect across clinical and preclinical settings. A human case series described three women who developed severe oral dryness and clinically reduced salivary secretion after receiving semaglutide for weight management. Oral examination showed minimal, frothy saliva. The reported modified Schirmer measurements have an unresolved unit inconsistency and are not interpreted quantitatively as salivary volume or flow rate (Table 1). Improvement following individualized management was descriptive and did not establish a causal relationship with semaglutide exposure. The pharmacovigilance analysis by Khan et al. [23] identified a disproportionate reporting signal for dry mouth associated with semaglutide. Because the analysis was based on spontaneous adverse-event reports, it did not provide incidence estimates or control for all potential clinical and reporting-related confounders. In contrast, exendin-4 improved salivary secretion in a D-galactose-induced aging model. Treatment preserved salivary acinar morphology, reduced the accumulation of acidic and neutral mucins, and decreased salivary-gland apoptosis. Thus, the available human evidence primarily identified potential treatment-associated salivary dysfunction, whereas the experimental animal evidence indicated a protective effect on salivary-gland structure and secretion in an aging-related injury model. No controlled prospective human studies objectively evaluating unstimulated or stimulated salivary flow during GLP-1 receptor agonist therapy were identified.

3.9. Oral and Peri-Implant Microbiome Findings

Direct evidence concerning the oral microbiome was scarce. The most comprehensive microbiome assessment was reported by Memida et al. [26] in diabetic mice with periodontal or peri-implant disease. Liraglutide shifted the periodontal oral microbiota toward the profile observed in normoglycemic controls. The intervention was also associated with changes in inflammatory and regulatory immune responses. Functional experiments using the recovered microbiota evaluated their capacity to induce cytokine responses. The

microbial response differed according to the oral site. Periodontal microbial communities showed greater responsiveness to liraglutide and the investigated anti-inflammatory interventions, whereas peri-implant communities were comparatively resistant to change. Beta-diversity differences were assessed using permutational multivariate analysis of variance. An additional study [25] evaluated a liraglutide-containing injectable hydrogel against Porphyromonas gingivalis and reported antibacterial activity. However, this single-species experimental assessment was distinct from a community-level oral microbiome analysis, and the antibacterial properties could not be attributed exclusively to systemic GLP-1 receptor activation. Overall, community-level oral microbiome evidence was represented by a very limited number of preclinical investigations. No prospective human oral or subgingival microbiome studies evaluating changes before and after GLP-1 receptor agonist initiation were identified.

3.10. Oral and Orofacial Adverse Events

Two large real-world datasets and one small case series contributed evidence concerning oral or orofacial adverse events. In a FAERS pharmacovigilance analysis, semaglutide showed reporting signals for dry mouth and dysgeusia, while liraglutide and exenatide showed signals for dysgeusia. These findings represented disproportionate reporting patterns rather than event incidence or confirmed drug-related causality. A multinational propensity-matched electronic-health-record study compared 226,485 GLP-1 receptor agonist users with an age- and sex-matched comparator cohort. Most of the evaluated orofacial outcomes were not increased among users, and several outcomes showed inverse associations. Gastroesophageal reflux disease was more frequent among exposed individuals, with a reported odds ratio of 1.329 (95% CI 1.291–1.367). Outcome-specific denominators varied following the exclusion of prevalent conditions, and the matching procedure was limited to age and sex. The semaglutide-associated hyposalivation case series provided additional clinical descriptions of severe dryness and reduced salivary secretion. Taken together, the available safety evidence identified potential signals related primarily to oral dryness and taste disturbance, but the designs did not establish incidence, dose–response relationships, or causality [22,23,45].

3.11. Findings According to the Investigated GLP-1 Receptor Agonist

Liraglutide had the broadest experimental evidence base and was evaluated in relation to periodontal inflammation, oxidative stress, osteoclast activity, osteogenic differentiation, periodontal regeneration, peri-implant bone formation, dental pulp stem-cell function, and local drug-delivery systems [39]. Its reported effects were predominantly anti-inflammatory, antioxidant, anti-resorptive, and pro-osteogenic.

Exendin-4 was investigated primarily in periodontal ligament stem cells, periodontal bone regeneration, orthodontic tooth movement, and salivary-gland injury. Most studies reported enhanced cellular migration, osteogenic differentiation, or tissue-regenerative responses [43], although locally administered high-dose exendin-4 inhibited orthodontic tooth movement.

Exenatide was studied mainly in experimental periodontitis and diabetic implant models. It reduced selected inflammatory mediators and enhanced peri-implant osteogenic responses; however, improvements in inflammatory markers were not consistently accompanied by reduced periodontal bone loss or collagen degradation [14].

Semaglutide was represented by a smaller and more recent evidence base encompassing both preclinical investigations and human safety observations. Experimental findings varied by model and intervention; regenerative outcomes from combination regimens should not be attributed to semaglutide alone [42]. Human pharmacovigilance data identi-

fied potential reporting signals for dry mouth and dysgeusia [23]. Owing to substantial heterogeneity in experimental models, doses, administration routes, treatment durations, comparators, and outcome definitions, direct comparisons among individual GLP-1 receptor agonists were not considered appropriate.

4. Discussion

This scoping review maps a predominantly preclinical body of evidence on the oral effects of GLP-1RAs, with limited direct human evidence. Its contribution should be considered alongside previous syntheses, which differ in their scope, eligibility criteria, and coverage of oral outcomes.

Jeong et al. searched PubMed, Embase, and the Cochrane Library to examine the broader relationship between periodontitis and GLP-1 pathways. Their eligibility criteria encompassed DPP-4 inhibitors and relevant scoping or systematic reviews, extending beyond original studies of GLP-1RA exposure [29]. Polymeri et al. searched MEDLINE/PubMed and Embase for English-language preclinical and clinical studies addressing periodontal mechanisms and emerging clinical implications. Their synthesis also incorporated human observations concerning endogenous incretin profiles; this evidence was considered indirect and insufficient to establish therapeutic benefit [30].

Henriques et al. searched PubMed/MEDLINE, Web of Science, Scopus, Embase, LILACS, and the Cochrane Library for studies evaluating GLP-1RA effects in periodontal tissues or models. They included seven preclinical studies and concluded that the evidence was insufficient to support a therapeutic indication [27]. In their systematic review, Nijakowski et al. searched PubMed, Web of Science, and Embase and synthesized human observational, animal, and in vitro evidence concerning periodontal inflammation and regeneration. Their reported eligibility criteria excluded case reports and other oral outcomes [28].

The present review searched PubMed, Scopus, and the Web of Science Core Collection and restricted eligibility to original studies in which a GLP-1RA was a principal intervention, exposure, or experimental factor. Studies limited to endogenous incretin concentrations or DPP-4-related biology without GLP-1RA exposure were therefore ineligible. Eligible designs included case reports, case series, and pharmacovigilance studies, allowing periodontal and regenerative findings to be considered alongside peri-implant, salivary, oral microbial, and orofacial adverse-event evidence. This broader oral perspective overlaps with narrative reviews by Sufaru et al. and Bijoch, which discuss mechanisms, oral-health implications, and considerations for dental care [31,32].

The contribution of the present review is the structured integration of original GLP-1RA exposure studies across these domains, with differentiation by agent, study design, and experimental or clinical context. Its conclusions align with previous periodontal syntheses in supporting biological plausibility while emphasizing the need for clinical validation [27–30].

Oral changes during GLP-1RA exposure may reflect local receptor-mediated actions, systemic metabolic improvements, or both. Findings from cellular models, non-diabetic animals, and local delivery systems support investigation of tissue-level mechanisms, but do not by themselves establish receptor specificity. Most studies did not isolate the contributions of glycemia, body weight, systemic inflammation, and local signaling; attribution of an oral outcome to a specific pathway therefore requires caution.

Modulation of periodontal inflammation was among the most consistent findings. Liraglutide reduced inflammatory-cell infiltration, macrophage accumulation, M1 polarization, pro-inflammatory mediator expression, osteoclast formation, and alveolar bone resorption in experimental periodontitis [12]. Exendin-4 attenuated LPS-induced TNF-α and IL-6 expression in periodontal ligament stem cells through NF-κB- and Wnt-related

signaling [13]. Molecular responses did not invariably coincide with preservation of periodontal structure. In the ligature-induced rat model reported by Moraes et al., exenatide reduced gingival Il1b, Mmp9, and Nos2 expression without a statistically significant reduction in alveolar bone loss or collagen degradation [14]. This illustrates why changes in inflammatory biomarkers alone are insufficient to infer tissue preservation within an experimental model or clinical benefit in humans.

The mechanistic spectrum extended beyond conventional cytokine suppression. Liraglutide enhanced Nrf2/HO-1-associated antioxidant responses and reduced oxidative and inflammatory injury in experimental periodontitis [47]. Semaglutide attenuated osteoblast ferroptosis through modulation of Wnt5a/Ror2/p38 MAPK signaling [41], whereas locally delivered liraglutide suppressed RIPK1/RIPK3/MLKL-associated necroptotic signaling in diabetic periodontal tissues [46]. In diabetic mice, liraglutide also modified RAGE- and IL-17A-related responses and restored Foxp3-positive regulatory T-cell representation in periodontal and peri-implant tissues [26]. Together, these findings suggest that GLP-1 receptor activation may influence interconnected pathways involving oxidative injury, regulated cell death, immune-cell balance, osteoclast activity, and tissue remodeling. Nevertheless, each pathway was demonstrated in a specific model, frequently with a single agonist and a limited set of experimental conditions. They should therefore be viewed as complementary mechanistic hypotheses rather than as established, interchangeable, or class-wide effects.

A second major pattern was the enhancement of osteogenic and regenerative competence. Liraglutide increased alkaline phosphatase activity, mineralized-matrix formation, and osteogenic-marker expression in periodontal ligament cells and bone-marrow stromal cells [19,40]. Exendin-4 partly reversed the impairment of proliferation, migration, mineralization, and osteogenic differentiation produced by high-glucose or inflammatory conditions in periodontal ligament stem cells [13,16]. More recent work implicated metabolic–epigenetic regulation, including H3K18 lactylation-dependent activation of DSPP, in liraglutide-induced dental pulp stem-cell differentiation [18]. However, concentration-dependent findings caution against assuming a linear relationship between exposure and benefit. In human alveolar bone-marrow stromal cells, liraglutide produced its most favorable response at 10^{-8} mol/L, whereas higher concentrations were detrimental to selected cellular outcomes [19]. Cell source, donor metabolic status, receptor expression, exposure duration, and local drug concentration are therefore likely to determine the magnitude and direction of response.

Local delivery represents a distinct translational strategy and should not be conflated with systemic GLP-1RA therapy used for diabetes or obesity. Liraglutide-containing PLGA/hydroxyapatite particles and an injectable carboxymethyl-chitosan–oxidized-dextran hydrogel improved inflammatory, osteogenic, and bone-regenerative outcomes in diabetic periodontal models [25,46]. A mechanistically different platform combined systemic semaglutide exposure with a metformin-loaded mesoporous polydopamine material rather than delivering semaglutide locally [42]. Because these systems contain active carriers or additional therapeutic agents, observed effects should be attributed to the complete intervention unless factorial designs isolate the contribution of each component. These studies support the feasibility of incorporating GLP-1RA-related signaling into combination regenerative strategies, but they do not demonstrate that conventional systemic dosing achieves equivalent periodontal exposure or therapeutic activity.

The peri-implant evidence broadly paralleled the osteogenic findings. In diabetic animal models, exenatide improved peri-implant bone microarchitecture, osteogenic activity, bone–implant integration, and biomechanical fixation, with evidence implicating LRP5/6/GSK-3β/β-catenin-related signaling [38]. Liraglutide also enhanced peri-implant bone formation in experimental models and promoted BMP2/Smad/Runx2-associated

osteogenesis in alveolar bone-marrow stromal cells [19]. Comparisons suggesting more favorable responses to exenatide than to insulin raise the possibility of osteomodulatory activity beyond glycemic lowering, but this interpretation remains provisional because equivalence in glycemic exposure, body weight, insulin sensitivity, and systemic inflammation cannot be assumed.

The retrospective clinical study by Shi et al. provided a preliminary human signal: marginal bone loss was lower among patients receiving GLP-1-based medication than among those treated with insulin or metformin at selected follow-up points [20]. Several design features limit causal interpretation. Treatment allocation reflected routine prescribing rather than randomization, creating potential confounding by indication and by differences in diabetes severity, duration, metabolic control, obesity, and comorbidity. Attrition substantially reduced the sample available at two years, and multiple implants were contributed by individual patients, requiring analytical methods that account for within-patient clustering. Moreover, radiographic differences were not accompanied by corresponding differences in probing depth or bleeding on probing. The study should therefore be interpreted as hypothesis-generating rather than as evidence that GLP-1RA therapy independently protects peri-implant tissues.

Salivary findings were limited and appeared directionally inconsistent only when viewed without regard to molecule, species, and biological context. A three-patient case series described severe oral dryness, minimal frothy saliva, and reduced secretion temporally associated with semaglutide treatment [22]. A FAERS analysis identified disproportionate reporting signals for dry mouth and dysgeusia with semaglutide and for dysgeusia with selected other GLP-1RAs, but such signals cannot establish incidence or causality [23]. Conversely, exendin-4 improved secretion, preserved acinar morphology, reduced mucin accumulation, and decreased salivary-gland apoptosis in a D-galactose-induced rat model of aging-related hyposalivation [24]. These findings are not directly contradictory: they involve different agonists, species, indications, doses, and mechanisms of salivary injury. A protective response in an experimentally injured rat gland cannot exclude treatment-associated oral dryness in humans, just as a small uncontrolled case series cannot establish a direct toxic effect of semaglutide on salivary tissue.

Clinical interpretation also requires a clear distinction between xerostomia, a subjective sensation of oral dryness, and hyposalivation, an objectively measured reduction in salivary secretion [21]. Gastrointestinal adverse effects, reduced fluid intake, dehydration, dietary change, concomitant xerogenic medications, and underlying metabolic disease could contribute to symptoms during GLP-1RA therapy. The modified Schirmer results require caution because of the reported unit inconsistency and should not be equated with standardized whole-saliva flow measurements. No prospective controlled human study with baseline and follow-up salivary measurements was identified. Consequently, the incidence, dose dependence, reversibility, and molecule-specific nature of any GLP-1RA-associated salivary effect remain undetermined.

Interpretation of the human safety findings is limited by the observational designs and potential biases. A large propensity-matched electronic-health-record analysis found no increased occurrence of most evaluated orofacial outcomes among GLP-1RA users and reported inverse associations for several outcomes, while gastroesophageal reflux disease was more frequent [45]. These associations should not be interpreted as protective or causal. Matching was limited to age and sex, outcome-specific denominators varied, and the analysis depended on diagnostic coding and clinical documentation. Similarly, FAERS is affected by underreporting, stimulated reporting, duplicate submissions, missing exposure denominators, incomplete clinical information, and confounding by indication. The available safety findings therefore warrant clinical awareness and prospective investigation,

but they do not provide reliable estimates of absolute risk or comparative safety across individual GLP-1RAs.

Despite the relevance of microbial dysbiosis to periodontal pathogenesis, the oral microbiome was one of the least developed evidence domains. In diabetic mice, liraglutide shifted periodontal microbial composition toward that observed in normoglycemic controls, and recovered microbial communities induced weaker inflammatory responses in coculture experiments; peri-implant communities appeared less responsive [26]. Because liraglutide simultaneously altered glycemia, inflammatory signaling, immune regulation, and tissue destruction, the study could not determine whether microbial changes reflected direct receptor-mediated effects or secondary ecological responses. Altered glucose availability, gingival inflammatory exudate, immune-selection pressures, and tissue integrity could each modify microbial composition. Conversely, changes in microbial communities could contribute to inflammatory attenuation, making causal direction impossible to establish from endpoint measurements alone. Antibacterial activity reported for a liraglutide-containing hydrogel against Porphyromonas gingivalis should also be distinguished from modulation of a complex microbial community, particularly because the carrier possessed intrinsic antibacterial and antioxidant properties [25]. The microbiome findings should therefore be regarded as preliminary mechanistic evidence rather than an established clinical effect.

Future research should prioritize prospective controlled human studies with baseline assessments and prespecified follow-up. Standardized clinical, radiographic, and patient-reported oral outcomes should be evaluated, with randomized treatment comparisons where clinically appropriate and feasible. Periodontal outcomes should include probing depth, clinical attachment level, bleeding on probing, plaque indices, and standardized radiographic measurements, while salivary assessment should incorporate validated xerostomia instruments and unstimulated and stimulated whole-saliva flow. HbA1c, body weight, smoking, diet, oral-hygiene behavior, concomitant medication, treatment indication, GLP-1RA dose, and exposure duration should be measured concurrently. Active-comparator designs involving other glucose-lowering or anti-obesity therapies would help distinguish effects associated with GLP-1 receptor agonism from those mediated by changes in glycemia or adiposity. Repeated measurements and appropriately specified mediation analyses may further clarify whether metabolic improvement, systemic inflammation, salivary function, or other pathways account for observed oral outcomes.

Microbiome investigations require longitudinal sampling, standardized periodontal-site selection, appropriate technical and negative controls, and integrated analysis of microbial composition, functional potential, inflammatory mediators, salivary variables, and clinical periodontal outcomes. Reporting should account for antibiotic exposure, diet, smoking, oral-hygiene practices, periodontal treatment, glycemic control, and sequencing batch effects; the STORMS framework offers a relevant reporting standard [50]. Implant studies should treat the patient as the principal analytical unit or use multilevel models when several implants are contributed by the same participant. Where randomization is not feasible, carefully designed longitudinal cohorts and target-trial emulations could improve causal interpretability by explicitly defining eligibility, treatment strategies, baseline, follow-up, outcomes, and causal contrasts [51].

This review has several strengths. It applied a structured scoping-review methodology, searched three major bibliographic databases, and integrated human, animal, in vitro, ex vivo, and mixed-design evidence across periodontal, peri-implant, salivary, microbial, regenerative, and adverse-event domains. Design-specific methodological appraisal was incorporated to contextualize evidence generated through fundamentally different research approaches. The accompanying bibliometric analysis additionally characterized the thematic and geographical development of the field, although its findings should be regarded

as exploratory because of the small corpus and sensitivity of network structure to individual publications and author-selected terminology.

Interpretation is limited by the predominance of preclinical evidence and substantial heterogeneity in species, metabolic status, disease models, agents, doses, administration routes, treatment durations, comparators, and outcome definitions. These differences limit cross-study comparability and do not support reliable comparisons of clinical efficacy among agents. Reporting of randomization, allocation concealment, blinding, and sample-size justification was frequently incomplete, limiting assessment of internal validity and precision. Unreported safeguards were not assumed to have been absent. Human findings were additionally constrained by residual confounding, selection and measurement biases, incomplete follow-up, and the limitations of spontaneous reporting.

Search sensitivity may have been affected by English-language and publication-type restrictions and the omission of exendin-4 as an explicit search term. Publication and selective-reporting biases may also have favored positive findings. These limitations restrict confidence in the magnitude, consistency, and clinical applicability of the mapped effects. Additional eligible studies indexed under terminology not captured by the search strategy may therefore have been missed. The findings should be interpreted as a synthesis of the retrieved evidence rather than an exhaustive account of all eligible studies.

Future research should prioritize well-designed prospective human studies capable of distinguishing direct GLP-1 receptor-mediated effects from improvements secondary to glycemic control, weight loss, and reductions in systemic inflammation. Standardized assessment of periodontal, peri-implant, salivary, and microbiome outcomes, together with detailed characterization of treatment exposure, metabolic status, and potential confounders, will be essential to improve comparability across studies. Longitudinal investigations integrating clinical, microbiological, salivary, and molecular endpoints may help clarify the mechanisms linking GLP-1RA therapy to oral health. Comparative studies across individual GLP-1RAs and emerging incretin-based therapies are also needed to determine whether observed effects represent class-wide phenomena or agent-specific responses.

5. Conclusions

This scoping review maps a predominantly preclinical and heterogeneous body of evidence on the oral effects of GLP-1RAs. Experimental findings support the biological plausibility of effects on periodontal and peri-implant tissues, but favorable molecular and cellular responses alone do not establish clinically meaningful tissue preservation. Human evidence remains limited and non-randomized, leaving therapeutic benefit and the causal interpretation of reported oral adverse events unresolved.

Accordingly, the available evidence does not justify recommending GLP-1RAs for periodontal treatment or selecting these agents to improve oral-health outcomes. Further investigation should prioritize prospective controlled human studies with standardized clinical, radiographic, and patient-reported outcomes, including objective assessments of salivary function where relevant. These studies should determine whether oral changes are sustained and clinically meaningful and clarify the contributions of glycemic control, body weight, and concomitant care.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/pharmaceutics18111410/s1: Table S1: Complete database-specific search strategies; Table S2: Reports excluded after full-text assessment and reasons.

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Abbreviations

The following abbreviations are used in this manuscript:

GLP-1	glucagon-like peptide-1
GLP-1RA(s)	glucagon-like peptide-1 receptor agonist(s)
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
OSF	Open Science Framework
DOI	Digital Object Identifier
PICOS	Population, Intervention, Comparator, Outcomes, and Study design
PMID	PubMed Identifier
URL	Uniform Resource Locator
JBI	Joanna Briggs Institute
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation
QUIN	Quality Assessment Tool for In Vitro Studies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GIP	glucose-dependent insulinotropic polypeptide
SD	standard deviation
IL-6	interleukin-6
TNF-α	tumor necrosis factor alpha
ANOVA	analysis of variance
ELISA	enzyme-linked immunosorbent assay
SPSS	Statistical Package for the Social Sciences
IL-1β	interleukin-1 beta
micro-CT	micro-computed tomography
RANKL	receptor activator of nuclear factor kappa-B ligand
OPG	osteoprotegerin
Runx2	runt-related transcription factor 2
ALP	alkaline phosphatase
mRNA	messenger ribonucleic acid
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
FAERS	FDA Adverse Event Reporting System
ROR	reporting odds ratio
PRR	proportional reporting ratio
CI	confidence interval

SEM	standard error of the mean
ARS	Alizarin Red S
BMSC(s)	bone marrow mesenchymal stem cell(s)
RT-PCR	reverse-transcription polymerase chain reaction
BMP2	bone morphogenetic protein 2
T2DM	type 2 diabetes mellitus
GK	Goto–Kakizaki
RNA-seq	RNA sequencing
GLP1R	glucagon-like peptide-1 receptor
GIPR	glucose-dependent insulinotropic polypeptide receptor
PDLSC(s)	periodontal ligament stem cell(s)
RIP-seq	RNA immunoprecipitation sequencing
ChIP-seq	chromatin immunoprecipitation sequencing
IFIT1/2/3	interferon-induced proteins with tetratricopeptide repeats 1, 2, and 3
TRAP	tartrate-resistant acid phosphatase
T2D	type 2 diabetes
PBS	phosphate-buffered saline
IHC	immunohistochemistry
LRP5/6	low-density lipoprotein receptor-related proteins 5 and 6
GSK-3β	glycogen synthase kinase 3 beta
BMPR1A	bone morphogenetic protein receptor type 1A
β-TrCP	beta-transducin repeat-containing protein
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
LPS	lipopolysaccharide
Wnt5a	Wnt family member 5A
EdU	5-ethynyl-2′-deoxyuridine
ROS	reactive oxygen species
MAPK	mitogen-activated protein kinase
CCK-8	Cell Counting Kit-8
Osx	osterix
NF-κB	nuclear factor kappa B
MPDA	mesoporous polydopamine
RNA	ribonucleic acid
DPSC(s)	dental pulp stem cell(s)
SDF-1	stromal cell-derived factor 1
hPDLC(s)	human periodontal ligament cell(s)
LSD	least significant difference
MMP-9	matrix metalloproteinase 9
NOS2	nitric oxide synthase 2
ICD-10	International Classification of Diseases, 10th Revision
GERD	gastroesophageal reflux disease
OR	odds ratio
RAGE	receptor for advanced glycation end products
Treg	regulatory T cell
PERMANOVA	permutational multivariate analysis of variance
ChIP	chromatin immunoprecipitation
DSPP	dentin sialophosphoprotein
RT-qPCR	reverse-transcription quantitative polymerase chain reaction
H3K18	histone H3 lysine 18
LIRA	liraglutide
PLGA/HA	Poly (lactic-co-glycolic acid)/hydroxyapatite
RIPK1	receptor-interacting serine/threonine-protein kinase 1
RIPK3	receptor-interacting serine/threonine-protein kinase 3
MLKL	mixed lineage kinase domain-like protein
CMCS-OD	carboxymethyl chitosan–oxidized dextran
TUNEL	terminal deoxynucleotidyl transferase dUTP nick-end labeling
Nrf2	nuclear factor erythroid 2-related factor 2
HO-1	heme oxygenase 1
MDA	malondialdehyde
GSH-Px	glutathione peroxidase

NQO1	NAD(P)H quinone oxidoreductase 1
ANCOVA	analysis of covariance
BGP	bone Gla protein
AMPK	AMP-activated protein kinase
HbA1c	glycated hemoglobin A1c
STORMS	Strengthening The Organization and Reporting of Microbiome Studies

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