

Efficacy of adjunctive hydrogel therapy in the management of peri-implant diseases: A systematic review

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Received July 6, 2026; Accepted September 28, 2026

DOI: 10.3892/wasj.2026.512

Abstract. Peri-implant diseases remain a critical challenge in implant dentistry, and adjunctive hydrogel therapy has emerged as a potential strategy to enhance conventional non-surgical management. The present systematic review assessed the efficacy of adjunctive hydrogel therapy, compared with conventional non-surgical therapy or other local adjuncts, in the management of peri-implant diseases, focusing on clinical, microbiological and radiographic outcomes reported in randomised controlled trials (RCTs). Conducted in accordance with the PRISMA 2020 guidelines and registered in PROSPERO (CRD420251163004), a search was performed on the PubMed, Scopus, Web of Science and Cochrane CENTRAL databases for studies published from 2011 to September, 2025, supplemented by hand-searching, grey-literature review and reference screening. Only human RCTs evaluating hydrogel-based adjuncts were eligible. Subsequently, two reviewers independently performed study selection, data extraction and risk-of-bias assessment using Cochrane RoB 2, and the certainty of evidence was rated using GRADE. A total of six reports from five RCTs (two reports sharing one peri-implantitis cohort), published between 2020 and 2025, were included. The hydrogels evaluated were 15% ozonated sunflower-oil hydrogel, 1.2% atorvastatin gel, a bio-adhesive antiseptic gel and 0.8% high-molecular-weight hyaluronic acid (HA), compared with 1% chlorhexidine gel, placebo/excipient gel, or mechanical debridement alone. Ozonated sunflower-oil hydrogel exhibited greater improvements in soft-tissue inflammation (bleeding on probing, bleeding score and suppuration) than chlorhexidine, whereas atorvastatin gel improved the clinical attachment level and pain on probing without a consistent reduction in bleeding on

probing, and HA additionally reduced crevicular IL-1 β and shifted the submucosal microbiome towards a less pathogenic profile. The bio-adhesive antiseptic gel and chlorhexidine achieved comparable clinical outcomes in their respective trial, though chlorhexidine caused soft-tissue and prosthetic staining. Adjunctive hydrogels appear to provide promising, although modest and inconsistent, benefits over mechanical debridement or chlorhexidine, mainly for inflammatory parameters, with very low to moderate certainty of evidence. Heterogeneity in formulations, protocols and follow-up durations, along with reliance on small single trials, limits firm conclusions. Standardised, longer-term RCTs are warranted to confirm these preliminary findings.

Introduction

Peri-implant diseases, which include peri-implant mucositis and peri-implantitis, are the most common biological complications associated with dental implants (1). Epidemiological data suggest that peri-implant mucositis affects ~46% of patients and peri-implantitis ~21% of patients (2,3). Peri-implantitis is characterised by inflammation of the peri-implant soft tissues with the progressive loss of supporting bone. Disease progression is influenced by microbial dysbiosis and the host inflammatory response, which ultimately compromise implant function and long-term survival (4,5). Implant failure is a multifactorial process, with contributing factors including patient age, smoking, systemic diseases, implant placement in the maxilla, and the quality and quantity of available bone (6). Despite advancements being made in implant-surface modification and surgical techniques, the management of peri-implant disease remains challenging owing to the complexity of biofilm accumulation and anatomical limitations (7).

Conventional non-surgical methods primarily involve mechanical debridement using curettes, ultrasonic instruments and air-abrasive devices, often combined with local antiseptics or systemic antibiotics. However, complete biofilm removal is difficult to achieve, particularly on rough implant surfaces, and mechanical therapy alone is often inadequate (8). Adjunctive approaches, such as chlorhexidine gels, photodynamic therapy and laser applications have been explored; however, their clinical benefits tend to be inconsistent or short-lived, with limited evidence of sustained regenerative effects. This variability highlights the need for adjunctive strategies that not

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Key words: peri-implant diseases, peri-implantitis, peri-implant mucositis, dental implants, hydrogels, non-surgical therapy

only reduce the microbial load, but also modulate inflammation and promote peri-implant tissue healing (9-11).

Hydrogels are promising adjunctive biomaterials owing to their biocompatibility, adaptable physicochemical properties and capacity to deliver bioactive substances in a controlled manner. These three-dimensional hydrophilic polymer networks can serve as scaffolds, drug-delivery systems, anti-microbial carriers and wound-healing promoters in peri-implant tissues (12-14). Of the various formulations, hyaluronic acid (HA)-based hydrogels have been particularly extensively studied due to the intrinsic anti-inflammatory, bacteriostatic and tissue-repair properties of HA. HA contributes to extracellular matrix stability, accelerates granulation tissue formation and modulates key inflammatory mediators, including interleukin (IL)-1 β and tumour necrosis factor- α (TNF- α), within peri-implant lesions (15). Several clinical studies have reported reductions in bleeding on probing, probing depth and local inflammatory markers following HA application (16,17). Other emerging materials include ozonated or oxygen-enriched hydrogels, such as ozonated sunflower-oil formulations, which combine the anti-microbial effects of ozone with the wound-modulating properties of lipid-based carriers (18). Ozone exhibits broad-spectrum anti-bacterial and anti-viral activity, disrupts biofilm architecture and enhances tissue oxygenation at sites of inflammation (19). In addition, bio-adhesive antiseptic hydrogels, atorvastatin-loaded hydrogels and chlorhexidine gels have been proposed as local adjuncts to peri-implant therapy. Bio-adhesive formulations enhance retention within peri-implant pockets and enable sustained anti-microbial release, while atorvastatin hydrogels provide local anti-inflammatory, anti-microbial and osteogenic effects that may support tissue regeneration (20-23). Collectively, these approaches aim to improve the outcomes of conventional therapy and enhance peri-implant tissue stability.

Despite growing interest in hydrogel-based adjuncts, the currently available evidence remains fragmented. Studies vary widely in hydrogel composition, concentration, dosing regimens, application protocols and outcome measures. Moreover, existing systematic reviews have often focused on single formulations, such as HA, or have included non-randomised study designs, thereby limiting the strength and clinical applicability of their conclusions (24,25). To date, to the best of our knowledge, no comprehensive systematic review has synthesised evidence from randomised controlled trials (RCTs) alone evaluating different hydrogel formulations as adjuncts to peri-implant therapy. Therefore, the present systematic review aimed to assess the efficacy of adjunctive hydrogel therapy compared with conventional or alternative methods for the management of peri-implant diseases, with an emphasis on clinical, microbiological and radiographic outcomes. By synthesising the current evidence from human RCTs, the present systematic review aimed to clarify the therapeutic potential of hydrogels and provide a foundation for standardised future research.

Data and methods

Protocol and registration. The present systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) 2020 statement (26). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration no. CRD420251163004).

Focused question. The focus of the present systematic review was to determine the efficacy of adjunctive hydrogel therapy compared with conventional therapy or other adjuncts in the management of peri-implant diseases.

PICO framework. The PICO framework was used as follows: Population: P₁ (peri-implant mucositis): Adults with ≥ 1 dental implant diagnosed with peri-implant mucositis (bleeding on probing, with or without suppuration, and no progressive marginal bone loss); P₂ (peri-implantitis): Adults with ≥ 1 dental implant diagnosed with peri-implantitis (probing pocket depth ≥ 4 mm, bleeding on probing and marginal bone loss > 2 mm). Intervention (I): Adjunctive hydrogel therapy. Comparator (C): Conventional non-surgical or surgical therapy, placebo/excipient gel, or other local adjuncts. Outcomes (O₁ peri-implant mucositis): Primary: Bleeding on probing; secondary: Probing pocket depth (PPD), plaque index, bleeding score, suppuration index, marginal mucosa condition and adverse events. Outcomes (O₂ peri-implantitis): Primary: PPD; secondary: Bleeding on probing, marginal bone loss, changes in inflammatory biomarkers (e.g., IL-1 β and TNF- α), submucosal microbiome composition and adverse events.

Eligibility criteria. Studies were included if they met all of the following criteria: RCT design; participants with peri-implant diseases; evaluation of a hydrogel-based adjunctive therapy; a comparison between interventions and/or a control group receiving placebo/excipient, standard therapy, or another adjunct; reporting of clinical parameters indicative of peri-implant disease; and availability of the full text in English. The exclusion criteria were the following: Non-randomised or observational studies, animal or *in vitro* studies, case reports, case series, reviews, letters and conference abstracts; studies not published in English; studies for which the full text was inaccessible; and studies not evaluating hydrogel interventions.

Information sources and search strategy. A systematic search of four electronic databases was performed: PubMed, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). The search combined Medical Subject Headings (MeSH) terms, free-text key words and Boolean operators (AND, OR), customised to each database, to retrieve articles published from January, 2011 to September, 2025. The applied filters were human studies, studies in the English language, and, where supported by the database interface, a study design limited to clinical trials or RCTs. The final search across all databases was conducted in September, 2025. The full electronic search strategy is presented in Table I. The hand-searching of six selected dental journals was performed to identify studies that may not have been indexed. Grey literature was searched using Google Scholar, preprint servers and clinical-trial registries (e.g., ClinicalTrials.gov), and requests were sent to experts in the field to retrieve potentially eligible unpublished studies. The reference lists of all eligible studies were hand-searched to ensure literature saturation. Records

Table I. Search strategy.

Database	Search terms/strategy
PubMed	(‘Peri-Implantitis’[MeSH] OR ‘peri-implantitis’[tiab] OR ‘peri-implant mucositis’[tiab] OR ‘peri-implant disease*’[tiab]) AND (‘Hydrogels’[MeSH] OR hydrogel*[tiab] OR gel[tiab] OR ‘hyaluronic acid’[tiab] OR ozon*[tiab] OR atorvastatin[tiab]). Filters: Humans; English; 2011-2025.
Scopus	TITLE-ABS-KEY[(‘peri-implantitis’ OR ‘peri-implant mucositis’ OR ‘peri-implant disease*’) AND (hydrogel* OR gel OR ‘hyaluronic acid’ OR ozon* OR atorvastatin)]. Limits: English; 2011-2025.
Cochrane CENTRAL	(‘peri-implantitis’ OR ‘peri-implant mucositis’ OR ‘peri-implant disease*’) AND (hydrogel* OR gel OR ‘hyaluronic acid’ OR ozon* OR atorvastatin) in Title/Abstract/Keyword (Trials). Limits: 2011-2025.
Web of Science	TS=((‘peri-implantitis’ OR ‘peri-implant mucositis’ OR ‘peri-implant disease*’) AND (hydrogel* OR gel OR ‘hyaluronic acid’ OR ozon* OR atorvastatin)). Languages: English; 2011-2025.
Boolean operators	AND/OR; truncation ; phrase searching with quotation marks.

were managed using Zotero reference-management software version 7.0.30 (<https://www.zotero.org>).

Data collection. Data were independently extracted by two authors (BG and RC) using custom-designed spreadsheets. The extracted data included author, year or publication, country, study design, intervention, comparator, outcome parameters and the conclusions of the study. Discrepancies were resolved by discussion with the full author team (BG, RC, NS and SS).

Risk-of-bias assessment. The risk of bias was assessed independently by two authors (BG and RC) during data extraction, with disagreements resolved by two additional authors (NS and SS). The Cochrane Risk of Bias 2 (RoB 2) tool for randomised trials was used (27). RoB 2 evaluates five domains: (D1) bias arising from the randomisation process; (D2) bias due to deviations from intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. Each domain and the overall judgement were categorised as ‘low risk’, ‘some concerns’ or ‘high risk’.

Certainty of evidence. The certainty of evidence was appraised using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach and summarised at the outcome level in a Summary of Findings table. Bodies of evidence from RCTs began at ‘high’ certainty and were downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias, yielding ratings of ‘very low’, ‘low’, ‘moderate’ or ‘high’ (28,29).

Results

Study selection. The selection process is summarised in the PRISMA 2020 flow diagram (Fig. 1) (24). Electronic searches identified 141 records. Following the removal of 49 duplicates, 92 titles and abstracts were screened, of which 64 were excluded as irrelevant, non-clinical, or lacking a hydrogel-based intervention. A total of 28 full-text articles were sought for retrieval; eight could not be obtained despite

attempts to access the articles through interlibrary loan, institutional subscriptions, Google Scholar and preprint servers. As their full texts were unavailable, the eligibility of these eight records could not be definitively determined, which is acknowledged as a limitation. Of the 20 full-text articles assessed for eligibility, 15 articles were excluded: Non-English language (n=3), non-clinical or *in vitro*/laboratory-based design (n=5), non-randomised or observational design (n=4) and insufficient or missing clinical data (n=3). Ultimately, six reports of five RCTs met the inclusion criteria; of note, Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31) report different outcomes from the same trial cohort.

Study characteristics. A total of six reports of five RCTs were included, published between 2020 and 2025, and conducted in Italy (32-34), Spain (30,31) and Iran (35). Sample sizes ranged from 18 to 61 patients. The number of implants or peri-implant sites evaluated varied with study design, from 100 implants in the peri-implantitis trial to 360 peri-implant mucositis sites in the largest split-mouth study. Participants were adults whose mean ages spanned the fifth and sixth decades (overall approximate range, 31-79 years).

Across the trials, adjunctive hydrogel therapy combined with mechanical debridement exhibited varying degrees of benefit. The two ozonated sunflower-oil hydrogel trials by Scribante *et al* (32) and Butera *et al* (33) reported greater reductions in soft-tissue inflammation, bleeding on probing, bleeding score and suppuration than with 1% chlorhexidine gel. Although probing depth reductions occurred in both study arms, hydrogel adjuncts generally produced more notable improvements in inflammation-related parameters rather than larger reductions in probing depth (32,33). Plaque index and marginal mucosal condition improved similarly in both study arms, with intergroup differences favouring the hydrogel that emerged only late in follow-up and were not sustained to the final visit in either trial; marginal bone level, assessed only in the 24-month trial, remained radiographically stable with no significant difference between the groups (32,33).

Storelli *et al* (34) compared a bio-adhesive antiseptic gel with 1% chlorhexidine and reported comparable clinical

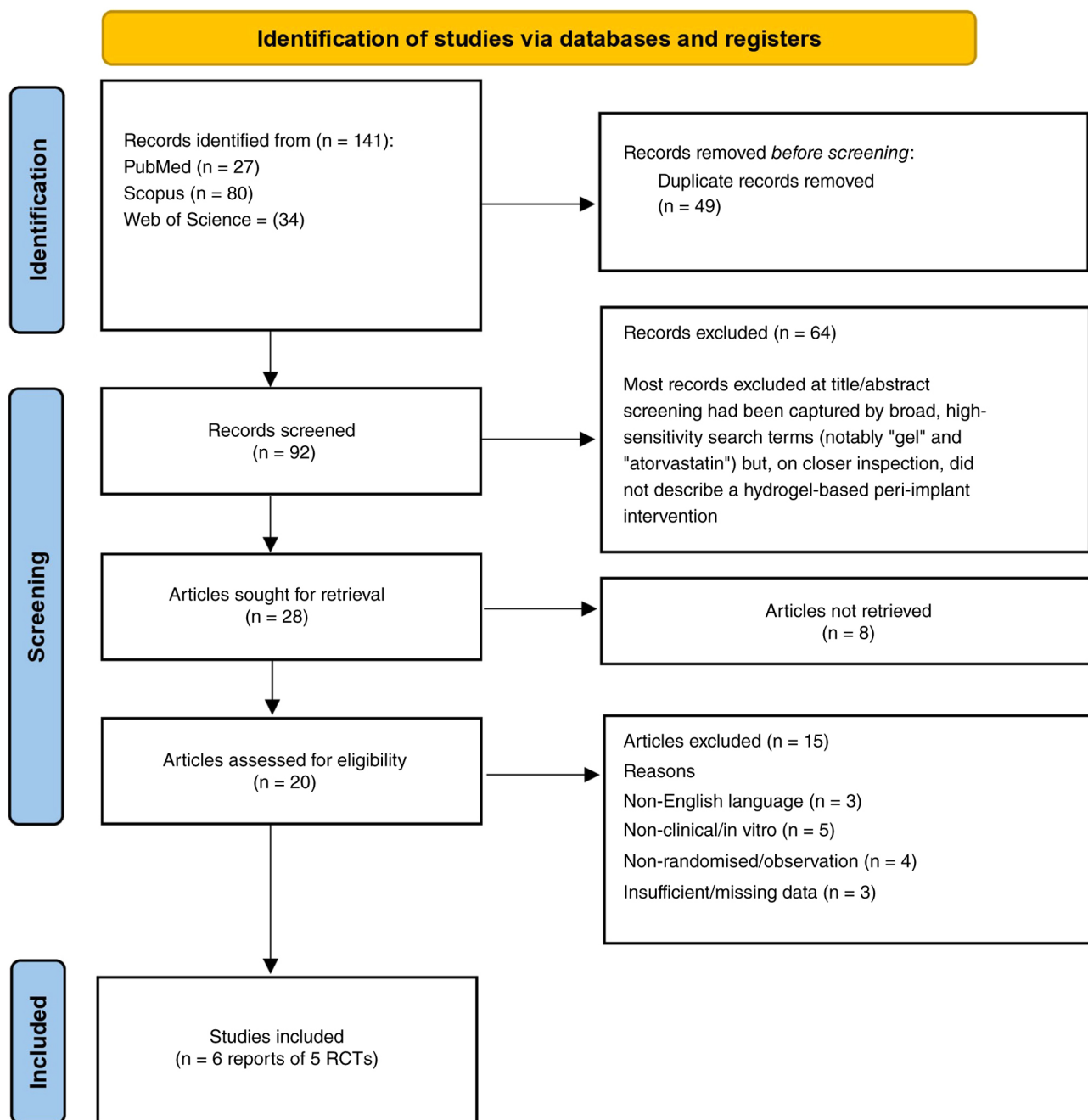


Figure 1. Flow diagram of included studies, based on PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials.

improvements between groups, with no meaningful difference in the modified bleeding index, plaque index, or proportion of implants achieving resolution of mucositis (67% with the bio-adhesive gel vs. 65% with chlorhexidine) over short-term follow-up; chlorhexidine was associated with soft tissue and prosthetic pigmentation, whereas the hydrogel was well-tolerated. A total of 21 patients were enrolled, and 18 patients were analysed after three dropouts (34).

Khorramdel *et al* (35) evaluated a 1.2% atorvastatin gel in peri-implant mucositis and reported statistically significant between-group improvements in the clinical attachment level and pain on probing compared with the placebo; however, a significantly worse (higher) bleeding-on-probing percentage compared with the placebo was observed at 3 months,

despite an initial reduction from baseline in both groups; although probing depth improved within both groups, the between-group difference was not statistically significant at 3 months ($P=0.25$). These findings suggest a host-modulatory effect when the gel is delivered submucosally following non-surgical debridement (35).

In the peri-implantitis trial investigating 0.8% high-molecular-weight HA (HMW-HA), Sánchez-Fernández *et al* (30) reported a statistically significant between-group reduction in probing depth favouring HA at 45 and 90 days, and significantly lower crevicular IL-1 β at sites with deeper pockets (PPD ≥ 5 mm); the reduction in bleeding on probing was a non-significant trend (30). The clinical attachment level and marginal bone level did not differ significantly between

Table II. Characteristics of the included studies.

Author(s), year of publication	Study design	Diagnosis/ study population	Test group intervention	Control group 1 intervention	Control group 2 intervention	No. of patients (total; test/control1/control2)	No. of implants or sites (total; test/control1/control2)	Follow-up duration	Age, mean $\pm$ SD (years)	(Refs.)
Scribante <i>et al</i> , 2026	Randomised, split-mouth, controlled clinical trial (single-centre); 24-month follow-up	Peri-implant mucositis	15% ozonated sunflower oil-based hydrogel (Ozoral Pro), in-office application + home use once daily for 14 days after each visit	1% chlorhexidine gel (Curasept Periodontal Gel), in-office application + home use once daily for 14 days after each visit	-	30 (split-mouth design; same 30 patients contributed sites to both groups)	360 total sites (180 test/180 control)	Baseline (T0), then T1-T9 at 1, 3, 6, 9, 12, 15, 18, 21, 24 months	Overall, 51.17 $\pm$ 10.03 (range, 35-77); split-mouth, same cohort for both arms	(32)
Khorramdel <i>et al</i> , 2024	Double-blinded (double-masked), parallel-group randomised controlled clinical trial	Peri-implant mucositis (severe) mucositis or mild peri-implantitis per inclusion criteria)	Mechanical debridement (MD) + 1.2% atorvastatin (ATV) gel injected into peri-implant pockets	Mechanical debridement (MD) + placebo gel	-	49 analysed of 54 randomised (test, 25/27 analysed; control, 24/27 analysed)	49 implants (one site/implant per patient)	Baseline, 1 month, 3 months	Overall sample aged 41-60 years (20 males, 29 females enrolled); group-specific baseline age not reported	(35)
Butera <i>et al</i> , 2023	Single-centre, split-mouth, randomised controlled trial (1:1 allocation)	Peri-implant mucositis	Ozonised hydrogel (Ozoral Gel/Ozoral Pro), in-office + home use once daily for 14 days	1% chlorhexidine gel (Curasept Periodontal Gel), in-office + home use once daily for 14 days	-	30 (split-mouth design; same 30 patients contributed sites to both groups)	180 total sites (90 test/90 control, per CONSORT diagram)	Baseline (T0), T1 (1 month), T2 (3 months), T3 (6 months)	Overall, 59.03 $\pm$ 8.31 (males, 59.14 $\pm$ 7.25; females, 58.94 $\pm$ 9.38); split-mouth, same cohort for both arms	(33)
Storelli <i>et al</i> , 2023	Randomised controlled clinical study; parallel-group (patient-level unit of analysis)	Peri-implant mucositis (probing depth >4 mm with bleeding on probing)	Bio-adhesive antiseptic gel (Gel made of Cetylpyridinium chloride, triclosan and essential oils)	1% chlorhexidine gel (Corsodyl) + 0.2% chlorhexidine mouthwash (Corsodyl)	-	18 analysed of 21 randomised (Test 10/11 analysed; control 8/10 analysed)	96 implants at baseline among analysed patients (test 53/control 43)	Baseline, 7, 15, 30 days, 2 months, 3 months	Overall mean 64 years (12 females, 9 males enrolled); group-specific baseline age not reported	(34)
Sánchez-Fernández <i>et al</i> , 2021	Double-blinded, controlled, randomised clinical trial; 3 parallel groups	Peri-implantitis (PPD $\geq$ 4 mm, bleeding on probing, radiographic marginal bone loss >2 mm)	0.8% high-molecular-weight hyaluronic acid (HMW-HA) gel, single in-office application + 0.2% gel applied by patient 3x/day at home for 45 days	Control 1: Exopolysaccharide (galactomannan) hydroxypropyl guar gel, applied by patient 3x/day at home for 45 days only (no in-office application)	Control 2: No topical application (dental-office or home)	61 analysed of 63 enrolled (test 21/control1 20/control2 20)	100 implants analysed of 104 placed (test, 32/control1, 32/control2, 36)	Baseline, 45 days, 90 days	Test, 60 $\pm$ 9; Control1, 64 $\pm$ 7; Control2, 58 $\pm$ 13	(30)

Table II. Continued.

Author(s), year of publication	Study design	Diagnosis/study population	Test group intervention	Control group 1 intervention	Control group 2 intervention	No. of patients (total; test/control1/control2)	No. of implants or sites (total; test/control1/control2)	Follow-up duration	Age, mean $\pm$ SD (years)	(Refs.)
Soriano-Lerma <i>et al</i> , 2020	Double-blinded, controlled, randomised clinical trial; 3 parallel groups (companion microbiome study of the same RCT registration, NCT03157193, as Sánchez-Fernández <i>et al</i>	Peri-implantitis	0.8% high-molecular-weight hyaluronic acid (HMW-HA) gel, in-office + 0.2% gel applied by patient 3x/day at home for 45 days	Control 1: Exopolysaccharide (hydroxypropyl guar galactomannan) placebo gel, patient-applied 3x/day at home for 45 days only	Control 2: No topical application	63 enrolled; 54 with paired baseline/45-day microbiome samples (test, 19/control1, 17/control2, 18)	104 implants placed (test, 32/control1, 34/control2, 38)	Baseline (t0), 45 days (t45)	Test, 60 $\pm$ 9; Control1, 64 $\pm$ 6; Control2, 58 $\pm$ 12	(31)

groups at 90 days, and crevicular TNF- α exhibited no significant between-group difference at 45 days (30). Reporting on the same cohort, Soriano-Lerma *et al* (31) found that HA was associated with a shift in the submucosal microbiome towards a less pathogenic profile.

Peri-implant mucositis was diagnosed on the basis of bleeding on probing and clinical inflammation without radiographic bone loss, whereas peri-implantitis required probing depths ≥ 4 –6 mm, bleeding-on-probing and/or suppuration, and marginal bone loss > 2 mm. All implants had been in function for at least 1 year prior to enrolment. The hydrogels assessed were a 15% ozonated sunflower-oil hydrogel, a bio-adhesive antiseptic gel, 1.2% atorvastatin gel and 0.8% HMW-HA gel. Application methods ranged from in-office topical and intra-pocket placement to home-use regimens, always following standardised mechanical debridement. Comparators were 1% chlorhexidine gel, placebo/excipient gels, or mechanical debridement alone, with identical oral-hygiene instructions across arms (30–35). Implant systems were generally not reported, apart from the HA peri-implantitis trial, which used Zimmer Tapered Swiss Plus[®] implants (30). Follow-up ranged from 45 days to 24 months; mucositis trials typically evaluated outcomes over 1–6 months (measuring clinical parameters up to 3 months within a 6-month study) and the peri-implantitis cohort over 45–90 days (30,31). Of note, two reports additionally measured IL-1 β and TNF- α in peri-implant crevicular fluid (30) and one analysed the submucosal microbiome (31) using 16S rRNA sequencing. The characteristics, baseline clinical parameters and outcomes of the included studies are summarised in Tables II–IV.

Risk of bias. The RoB 2 judgements are presented in Fig. 2. Khorramdel *et al* (35) were judged at low risk across all five domains. The remaining studies raised ‘some concerns’ overall, attributable to specific domains: Scribante *et al* (32) and Butera *et al* (33) to deviations from intended interventions (D2) and measurement of the outcome (D4), reflecting the open-label split-mouth design; Butera *et al* (33) additionally to selection of the reported result (D5); Scribante *et al* (32) to the randomisation process (D1), missing outcome data (D3; three dropouts), measurement of the outcome (D4), and selective reporting (D5); Sánchez-Fernández *et al* (30) to missing outcome data (D3); and Soriano-Lerma *et al* (31) to missing outcome data (D3) and selective reporting (D5). In maintaining the RoB 2 rules, an overall judgement of ‘some concerns’ was assigned when at least one domain raised concerns and no domain was at high risk. The summary plot (Fig. 3) demonstrates that the body of evidence is largely characterised by an overall RoB 2 judgement of ‘some concerns’, driven primarily by missing outcome data and potential biases in outcome measurement and selective reporting. This limitation should be considered when interpreting the effect estimates (27).

Certainty of evidence. Outcome-level GRADE ratings are summarised in the summary of findings table (Table V). As each outcome was rated individually against the five GRADE domains rather than assigned a uniform level, ratings ranged from very low to moderate across outcomes, reflecting differences in risk of bias, inconsistency, indirectness and imprecision rather than a fixed ceiling tied to trial

Table III. Baseline clinical parameters of the included studies.

Author(s), year of publication	Study groups	Clinical parameter (scale/unit)	Control group (baseline)	Test group (baseline)	Control group 2 (baseline)	(Refs.)
Scribante <i>et al</i> , 2026	1% chlorhexidine gel (control); 15% ozonated sunflower oil-based hydrogel (test)	Probing pocket depth (PPD), mm	6.55±1.18	6.82±1.24		(32)
		Plaque index (PI), 0-1 (presence)	1.00±0.00	1.00±0.00		
		Bleeding on probing (BoP), 0-1 (presence)	1.00±0.00	1.00±0.00		
		Bleeding score (BS), 0-3	2.13±0.66	2.07±0.70		
		Suppuration index (SI), 0-1	0.16±0.37	0.17±0.38		
		Marginal mucosal condition (MMC), 0-3	2.29±0.49	2.29±0.48		
		Marginal bone level (MBL), mm	1.30±0.92	1.21±0.69		
Khorramdel <i>et al</i> , 2024	Mechanical debridement (MD) + placebo gel (control); Mechanical debridement (MD) + 1.2% atorvastatin (ATV) gel (test)	Bleeding on probing (BOP), %	76.6±15.2	79.4±13.2		(35)
		Probing depth (PD), mm	5.4±0.7	5.4±0.6		
		Clinical attachment level (CAL), mm	6.0±0.7	6.9±0.8		
		Pain on probing (POP), cm (VAS)	5.5±1.7	4.5±1.4		
		Probing depth (PD), mm	6.55±1.18	6.80±1.21		
		Plaque index (PI), %	84.93±16.74	84.27±16.24		
		Bleeding on probing (BoP), %	44.62±26.94	46.14±27.09		
Butera <i>et al</i> , 2023	1% chlorhexidine gel (control); Ozonised hydrogel (test)	Suppuration index (SI), 0-1	0.16±0.37	0.17±0.38		(33)
		Bleeding score (BS), 0-3	2.13±0.66	2.05±0.71		
		Marginal mucosal condition (MMC), 0-3	2.29±0.49	2.27±0.47		
		Implants contributed, n	43	53		
		Modified bleeding index (mBI), 0-3	1.53±0.19	1.16±0.35		
		Plaque index (PI), 0-3	1.59±0.64	1.57±0.69		
		Bleeding on probing (BOP), %	100	100	100	
Storelli <i>et al</i> , 2023	1% chlorhexidine gel (control); Bio-adhesive antiseptic gel (gel made of Cetylpyridinium chloride, triclosan and essential oils) (test)	Probing pocket depth (PPD), mm	4.21±1.14	3.62±0.83	3.67±0.72	(30)
		Clinical attachment loss (CAL), mm	4.37±1.32	4.06±1.40	3.74±0.76	
		Marginal bone loss (MBL), mm	3.56±2.01	3.41±1.66	3.40±0.91	
		IL-1β (pg/ml)	77±95	74±91	74±81	
		TNF-α (pg/ml)	0.35±0.30	0.31±0.39	0.32±0.31	
		Bleeding on probing (BOP), %	100	100	100	
		Probing depth (PD), mm	5.47±1.26	4.81±0.96	4.84±0.89	
Sanchez-Fernandez <i>et al</i> , 2021	Exopolysaccharide (galactomannan) hydroxypropyl guar gel (control 1); 0.8% high-molecular-weight hyaluronic acid (HMW-HA) gel (test); No topical application (control 2)	Clinical attachment loss (CAL), mm	5.71±1.36	5.28±1.40	4.92±0.94	(31)
		Marginal bone level (MBL), mm	3.92±2.05	3.77±2.33	3.63±0.95	
		InvSimpson diversity index (submucosal 16S rRNA), Stratum 3, n=28 sites	6.42	10.16	4.18	
		Shannon diversity index (submucosal 16S rRNA), Stratum 3, n=28 sites	2.75	3.28	2.29	
		Pielou evenness index (submucosal 16S rRNA), Stratum 3, n=28 sites	0.58	0.64	0.48	
			(IQR, 0.15)	(IQR, 0.07)	(IQR, 0.15)	
Soriano-Lerma <i>et al</i> , 2020	Exopolysaccharide (galactomannan) hydroxypropyl guar gel (control 1); 0.8% high-molecular-weight hyaluronic acid (HMW-HA) gel (test); No topical application (control 2)	Bleeding on probing (BOP), %	100	100	100	(31)
		Probing depth (PD), mm	5.47±1.26	4.81±0.96	4.84±0.89	
		Clinical attachment loss, mm	5.71±1.36	5.28±1.40	4.92±0.94	
		Marginal bone level (MBL), mm	3.92±2.05	3.77±2.33	3.63±0.95	
		InvSimpson diversity index (submucosal 16S rRNA), Stratum 3, n=28 sites	6.42	10.16	4.18	
		Shannon diversity index (submucosal 16S rRNA), Stratum 3, n=28 sites	2.75	3.28	2.29	
		Pielou evenness index (submucosal 16S rRNA), Stratum 3, n=28 sites	0.58	0.64	0.48	

Table IV. Clinical outcomes of the included studies.

Author(s), year of publication	Study groups	Follow-up period	Clinical parameter (scale/unit)	Control group outcome	Test group outcome	Control group 2 outcome	Inference	(Refs.)
Scribante <i>et al</i> , 2026	1% chlorhexidine gel (control); 15% ozonated sunflower oil-based hydrogel (test)	24 months (T9)	Probing pocket depth, mm	3.72±0.86	2.95±0.94		Significant reduction from baseline in both groups (P<0.05). Test group significantly lower than Control from T7 (18 months) onward, including at T9 (P<0.05).	(32)
		24 months (T9)	Plaque index, 0-1 (presence)	0.30±0.46	0.04±0.20		Significant intragroup reduction in both. No intergroup difference up to T6; Test group significantly lower than Control from T7 onward, including T9 (P<0.05).	
		24 months (T9)	Bleeding on probing, 0-1	0.11±0.32	0.00±0.00		Significant intragroup reduction in both. No intergroup difference up to T8; a significant advantage for Test group emerged at T9 (P<0.05).	
		24 months (T9)	Bleeding score, 0-3	0.53±0.50	0.07±0.25		Significant intragroup reduction in both. Test group significantly lower at T3 and from T6 (15 months) through T9 (P<0.05).	
		24 months (T9)	Suppuration index, 0-1	0.00±0.00	0.00±0.00		Both groups reached complete resolution of suppuration; no significant intergroup difference at any time point (P>0.05).	
		24 months (T9)	Marginal mucosal condition, 0-3	0.43±0.50	0.03±0.16		Significant intragroup reduction in both groups. Intergroup difference significant only at T7 and T8 (P<0.05); not reported as significant at T9.	
		24 months (T9)	Marginal bone level, mm	1.29±0.91	1.12±0.64		Both groups remained radiographically stable, with no progression to peri-implantitis; no significant difference between or within groups over time (Kruskal-Wallis P=0.9932).	

Table IV. Continued.

Author(s), year of publication	Study groups	Follow-up period	Clinical parameter (scale/unit)	Control group outcome	Test group outcome	Control group 2 outcome	Inference	(Refs.)
Khorramdel <i>et al</i> , 2024	Mechanical debridement (MD) + placebo gel (control); mechanical debridement (MD) + 1.2% atorvastatin (ATV) gel (test)	3 months	Bleeding on probing, %	29.4±9.4	49.1±15.4		Significant reduction from baseline in both groups ($P<0.0001$). At 3 months, BOP% was significantly higher in the Test/ATV group than the Control group (intergroup $P=0.0001$) - BOP rebounded between 1 and 3 months in the ATV group. Significant intragroup reduction in both groups ($P<0.0001$). Intergroup difference significant at 1 month ($P=0.004$) but not at 3 months ($P=0.252$). Test group improved significantly at both follow-ups ($P<0.0001$); Control's change was significant at 1 month only (not sustained at 3 months, $P=0.426$). Intergroup difference significant throughout ($P<0.0001$), favouring Test - interpret cautiously given a significant baseline imbalance (Control 6.0 ± 0.7 vs. Test 6.9 ± 0.8 mm). Test group improved significantly at both follow-ups ($P\leq0.05$); Control group improvement was significant at 1 month only (not sustained at 3 months, $P=0.862$). Intergroup difference significant at both follow-ups ($P=0.001$), favouring the Test group.	(35)
		3 months	Probing depth, mm	3.6±0.8	3.4±0.6			
		3 months	Clinical attachment level, mm	5.9±0.6	4.6±0.5			
		3 months	Pain on probing, cm (VAS)	5.6±1.7	3.6±1.0			
Butera <i>et al</i> , 2023	1% chlorhexidine gel (control); ozonised hydrogel (test)	6 months (T3)	Probing depth, mm	4.23±1.13	3.92±1.42		Significant intragroup reduction in both groups ($P<0.05$); no significant intergroup difference at any time point, including T3 ($P>0.05$).	(33)

Table IV. Continued.

Author(s), year of publication	Study groups	Follow-up period	Clinical parameter (scale/unit)	Control group outcome	Test group outcome	Control group 2 outcome	Inference	(Refs.)
Storelli <i>et al</i> , 2023	1% chlorhexidine gel (control); Bio-adhesive antiseptic gel (gel made of cetylpyridinium chloride, triclosan and essential oils) (test)	6 months (T3)	Plaque index, %	47.20±19.43	42.03±21.13		Significant intragroup reduction in both groups. Intergroup difference significant only at T2 (3 months, P<0.05), favouring Test group; not sustained at T3.	(34)
		6 months (T3)	Bleeding on probing, %	18.57±15.86	9.95±7.17		Significant intragroup reduction in both groups. Test group significantly lower than Control at T1, T2 and T3 (P<0.05).	
		6 months (T3)	Suppuration index, 0-1	0.04±0.20	0.02±0.16		Significant intragroup reduction in both groups; no significant intergroup difference at any time point (P>0.05).	
		6 months (T3)	Bleeding score, 0-3	1.31±0.68	0.85±0.67		Significant intragroup reduction in both groups. Test group significantly lower than Control at T2 and T3 (P<0.05).	
		6 months (T3)	Marginal mucosal condition, 0-3	1.09±0.68	0.96±0.72		Significant intragroup reduction in both groups; no significant intergroup difference at any time point (P>0.05).	
		3 months	Modified bleeding index, 0-3	0.49±0.25	0.29±0.28		Both groups improved substantially from baseline (mean reduction 68.2% Control vs. 71.0% Test); final mBI and % improvement did not differ significantly between groups (NS, Wilcoxon rank-sum with continuity correction).	
		3 months	Plaque index, 0-3	0.56±0.30	0.67±0.43		Both groups improved from baseline (mean reduction 64.1% Control vs. 58.4% Test); final PI and % improvement did not differ significantly between groups (NS).	
		3 months	Implants healed, n (%)	28/43 (65%)	36/53 (67%)		Similar proportion of implants achieved resolution of mucositis/bleeding in both groups; no significant difference (Fisher's exact test, NS).	

Table IV. Continued.

Author(s), year of publication	Study groups	Follow-up period	Clinical parameter (scale/unit)	Control group outcome	Test group outcome	Control group 2 outcome	Inference	(Refs.)
Sanchez-Fernandez <i>et al.</i> , 2021	Exopolysaccharide (galactomannan) hydroxypropyl guar gel (control 1); 0.8% high-molecular-weight hyaluronic acid (HMW-HA) gel (test); No topical application (control 2)	90 days	Bleeding on probing, %	28.1	15.6	38.9	Greater reduction in Test group (HA) group than either control at 90 days; differences not statistically significant (Test vs. Control1 P=0.29; Test vs. Control2 P=0.07, borderline; Control1 vs. Control2, P=0.68 at 45 days/0.43 at 90 days). Test group significantly lower than Control1 at 90 days (P=0.01) and at 45 days (P=0.01); Test vs. Control2 not significant (P=0.16); Control1 vs. Control2 not significant (P=0.18). No significant difference between any pair of groups at 90 days (all P>0.05).	(30)
		90 days	Probing pocket depth, mm	3.63±1.01	2.97±0.64	3.25±0.78	MBL remained stable in the Test group and increased slightly in both control groups; no significant difference between groups at 90 days (all P>0.05).	
		90 days	Clinical attachment loss, mm	3.79±1.24	3.45±1.49	3.29±0.75		
		90 days	Marginal bone loss, mm	3.66±2.04	3.39±1.70	3.43±0.89		
		45 days (not measured at 90 days)	IL-1 β (pg/ml)	66±65	65±77	84±92	No significant difference between groups overall at 45 days (all P>0.05); among implants with baseline PPD $\geq$ 5 mm, Test group exhibited significantly greater IL-1 β reduction than Control2 (P=0.04).	
		45 days (not measured at 90 days)	TNF- α (pg/ml)	0.22±0.45	0.16±0.40	0.24±0.37	No significant difference between groups at 45 days (all P>0.05).	

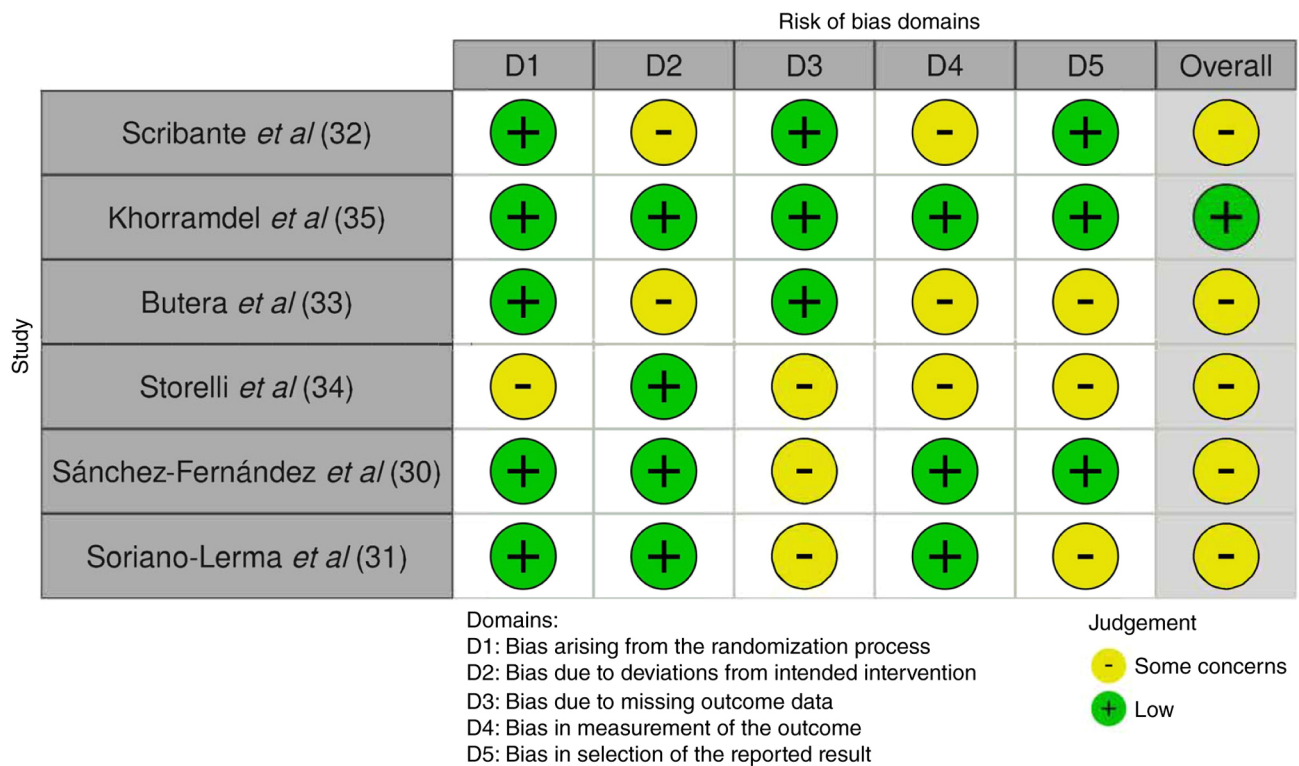


Figure 2. RoB-2 risk of bias assessment. RoB-2, risk of bias tool 2.

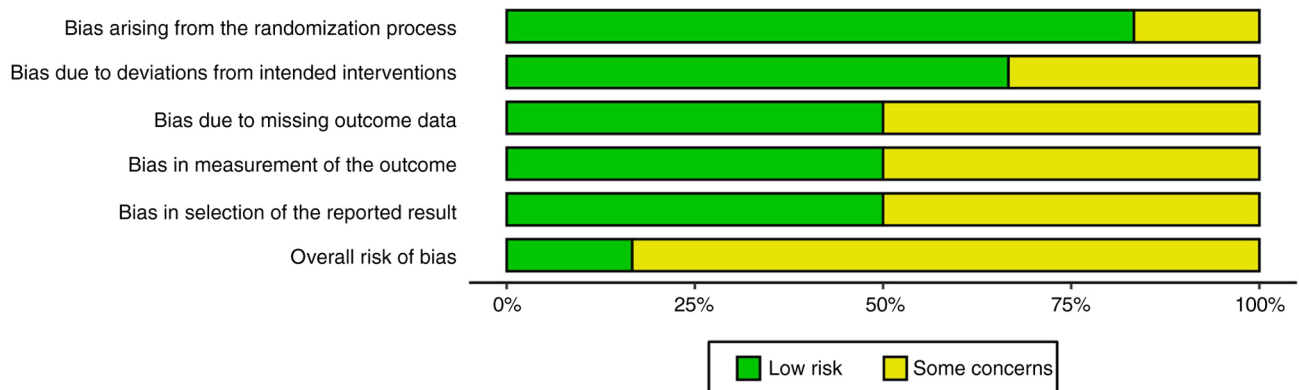


Figure 3. Collective data (%) for risk of bias, according to RoB-2 domains (summary plot). RoB-2, risk of bias tool 2.

count. Moderate certainty (downgraded one level) applied to bleeding on probing and other inflammatory parameters for the ozonated-hydrogel-versus-chlorhexidine comparison (downgraded for risk of bias) and to bleeding on probing, clinical attachment level, and pain on probing for atorvastatin vs. the placebo (downgraded for imprecision). Low certainty applied to the probing-depth comparisons for the ozonated and atorvastatin gels (inconsistent or non-significant between-group effects) and to the comparison of the bio-adhesive gel vs. chlorhexidine, which exhibited no statistically significant between-group difference (small single trial, downgraded for imprecision). Outcomes for hyaluronic acid in peri-implantitis ranged from low to very low certainty, reflecting the single trial cohort with short follow-up and, for several outcomes, further downgrading for indirectness or imprecision. No outcome reached high certainty (28,29).

Discussion

The present systematic review synthesised evidence from six reports of five RCTs evaluating hydrogel-based adjuncts in peri-implant mucositis and early peri-implantitis. Within the limits of very low to moderate-certainty evidence, the included trials suggest that ozonated sunflower-oil hydrogel and HMW-HA gel may provide additional benefit in reducing peri-implant soft-tissue inflammation when used alongside mechanical debridement, whereas atorvastatin gel exhibited benefit for clinical attachment level and pain on probing without a consistent reduction in bleeding on probing. This reflects growing interest in bioactive gel formulations as minimally invasive adjuncts that can locally modulate inflammation, interfere with biofilm organisation, and support soft-tissue healing around implants.

Table V. Summary of evidence quality across studies (GRADE).

Outcome	Comparison (population)	Studies participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (GRADE)	Absolute effect	Summary statement	(Refs.)
Bleeding on probing/ bleeding indices (BoP, bleeding score) 6 mo (33); 24 mo	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	60 patients (2 RCTs)	Serious	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ MODERATE	Butera <i>et al</i> (33) (6 mo, BoP%); control 18.6%; MD 8.6 pp fewer with hydrogel (95% CI 5.0 to 12.2 fewer) Scribante <i>et al</i> (32) (24 mo, bleeding score 0-3); control 0.53; MD 0.46 points fewer with hydrogel (95% CI, 0.38 to 0.54 fewer)	Ozonated hydrogel may provide greater reductions in bleeding-related parameters than chlorhexidine gel, with both trials demonstrating statistically significant differences favouring the hydrogel. However, the clinical relevance of these findings remains uncertain, as a minimally important clinical difference has not yet been established.	(32)
Probing pocket depth (PPD) 6 mo (33); 24 mo	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	60 patients (2 RCTs)	Serious	Serious	Not serious	Not serious	Undetected	⊕⊕⊕ LOW	Scribante <i>et al</i> (32) (24 mo): control 3.72 mm; MD 0.77 mm lower with hydrogel (95% CI 0.58 to 0.96 lower), significant only from 18 mo; Butera <i>et al</i> (33) (6 mo): control 4.23 mm; MD 0.31 mm lower (95% CI 0.06 higher to 0.68 lower), not significant	May reduce probing depth, but the benefit was not consistent across the two trials or follow-up durations; true effect uncertain.	(32)
Plaque index (PI) 6 mo (33); 24 mo	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	60 patients (2 RCTs)	Serious	Serious	Not serious	Not serious	Undetected	⊕⊕⊕ LOW	Scribante <i>et al</i> (32) (24 mo, 0-1 scale): control 0.30; MD 0.26 lower with hydrogel (95% CI 0.19 to 0.33 lower) Butera <i>et al</i> (33) (6 mo, %): control 47.2%; MD 5.2 pp lower (95% CI 0.8 higher to 11.1 lower), not significant	Effect on plaque control is inconsistent between trials and time-points [significant only late in Scribante <i>et al</i> (32), only at an interim visit in Butera <i>et al</i> (33); certainty is low].	(32)
Suppuration index (SI) 6 mo (33); 24 mo	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	60 patients (2 RCTs)	Serious	Not serious	Not serious	Serious	Undetected	⊕⊕⊕ LOW	Both trials: suppuration resolved to near-zero in both arms by final follow-up [Scribante <i>et al</i> (32), 24 mo: 0.00 vs. 0.00; Butera <i>et al</i> (33), 6 mo: control 0.04, MD 0.02 lower, 95% CI 0.03 higher to 0.07 lower]	No important between-group difference detected; very low event rates in both arms limit ability to detect a true difference.	(32)

Table V. Continued.

Outcome	Comparison (population)	Studies participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (GRADE)	Absolute effect	Summary statement	(Refs.)
Marginal mucosal condition (MMC) (24 mo)	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	30 patients (1 RCT)	Serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ LOW	Control 0.43 (0-3 scale); MD 0.40 lower with hydrogel (95% CI 0.32 to 0.48 lower) - trial's own analysis found this not significant at 24 mo	Naïve CI appears to exclude no effect, but the trial's own repeated-measures analysis found no significant difference at the final visit; interpret cautiously.	(32)
Marginal bone level/stability (MBL) (24 mo)	15% Ozonated sunflower-oil hydrogel + mechanical debridement vs. 1% chlorhexidine gel + mechanical debridement (peri-implant mucositis)	30 patients (1 RCT)	Serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ LOW	Control 1.29 mm; MD 0.17 mm lower with hydrogel (95% CI 0.01 to 0.33 lower)-trial's own test found no significant difference (P=0.99)	Bone levels remained radiographically stable in both groups; no clinically important difference detected.	(32)
Clinical attachment level (CAL) (3 mo)	1.2% Atorvastatin gel + mechanical debridement vs. placebo gel + mechanical debridement (peri-implant mucositis)	49 patients (1 RCT)	Not serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ MODERATE	Control 5.9 mm; MD 1.3 mm lower (better) with atorvastatin (95% CI 0.99 to 1.61 lower)	Probably improves CAL more than placebo. Note: atorvastatin group had significantly worse baseline CAL (6.9 vs. 6.0 mm)	(35)
Pain on probing (POP, VAS) (3 mo)	1.2% Atorvastatin gel + mechanical debridement vs. placebo gel + mechanical debridement (peri-implant mucositis)	49 patients (1 RCT)	Not serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ MODERATE	Control 5.6 cm; MD 2.0 cm lower (better) with atorvastatin (95% CI 1.21 to 2.79 lower)	Probably reduces pain on probing more than placebo.	(35)
Bleeding on probing (BOP, %) (3 mo)	1.2% Atorvastatin gel + mechanical debridement vs. placebo gel + mechanical debridement (peri-implant mucositis)	49 patients (1 RCT)	Not serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ MODERATE	Control 29.4%; MD 19.7 pp HIGHER (worse) with atorvastatin (95% CI 12.6 to 26.8 higher)	Control 29.4±9.4% vs. atorvastatin 49.1±15.4% at 3 mo, P=0.0001, shows BOP significantly worse with atorvastatin, after a rebound between months 1 and 3.	(35)

Table V. Continued.

Outcome	Comparison (population)	Studies participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (GRADE)	Absolute effect	Summary statement	(Refs.)
Probing depth (PD) (3 mo)	1.2% Atorvastatin gel + mechanical debridement vs. placebo gel + mechanical debridement (peri-implant mucositis)	49 patients (1 RCT)	Not serious	N/A (single trial)	Not serious	Very serious	Undetected	⊕⊕⊕⊕ LOW	Control 3.6 mm; MD 0.2 mm lower with atorvastatin (95% CI 0.20 higher to 0.60 lower), not significant (P=0.25)	Probably little or no difference in probing depth at 3 months; evidence very uncertain (single small trial, non-significant).	(35)
Modified bleeding index (mBI) (3 mo)	Bio-adhesive antiseptic gel vs. 1% chlorhexidine gel (peri-implant mucositis)	18 patients (1 RCT)	Serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ LOW	Control 0.49 (0-3 scale); MD 0.20 lower with bio-adhesive gel (95% CI 0.05 higher to 0.45 lower), not significant	Little or no difference for bleeding reduction. Groups differed significantly at baseline (initial mBI: control 1.53 vs. test 1.16, P=0.025), consistent with 'some concerns' on randomisation (D1).	(34)
Plaque index (PI) (3 mo)	Bio-adhesive antiseptic gel vs. 1% chlorhexidine gel (peri-implant mucositis)	18 patients (1 RCT)	Serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ LOW	Control 0.56 (0-3 scale); MD 0.11 higher (numerically worse) with bioadhesive gel (95% CI 0.23 lower to 0.45 higher), not significant	No important difference detected in plaque control between the two gels.	(34)
Implants achieving resolution of mucositis ('implants healed') (3 mo)	Bio-adhesive antiseptic gel vs. 1% chlorhexidine gel (peri-implant mucositis)	18 patients/ 96 implants (1 RCT)	Serious	N/A (single trial)	Not serious	Serious	Undetected	⊕⊕⊕⊕ LOW	651 per 1000 with chlorhexidine; 28 more per 1000 with bio-adhesive gel (95% CI 162 fewer to 218 more)	Probably little or no difference in proportion healed. Chlorhexidine caused visible tooth/prosthetic staining not seen with the bio-adhesive gel (adverse effect, not formally graded).	(34)
Probing pocket depth (PPD)-HA vs. excipient gel (C1) (90 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Not serious	Undetected	⊕⊕⊕⊕ LOW	Control 1 (excipient) 3.63 mm; MD 0.66 mm lower with HA (95% CI 0.54 to 1.72 lower)	May reduce probing depth more than excipient gel alone at 90 days, but evidence is from one small, short-follow-up trial.	(30)
Probing pocket depth (PPD)-HA vs. no treatment (C2) (90 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Serious	Undetected	⊕⊕⊕⊕ VERY LOW	Control 2 (no treatment) 3.25 mm; MD 0.28 mm lower with HA (95% CI 0.15 to 1.13 lower)	May reduce probing depth vs. no treatment, but this comparator was unblinded (no product applied), and the estimate is imprecise; certainty very low.	(30)

Table V. Continued.

Outcome	Comparison (population)	Studies participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty (GRADE)	Absolute effect	Summary statement	(Refs.)
Bleeding on probing (BOP)-HA vs. excipient/no treatment (90 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Serious	Undetected	⊕⊕⊕⊕ VERY LOW	vs. CI: control 281/1000; 125 fewer/1000 with HA (95% CI 325 fewer to 75 more) vs. C2: control 389/1000; 233 fewer/1000 with HA (95% CI 436 fewer to 30 fewer)-borderline (P=0.07)	May reduce BOP vs. no treatment (borderline); difference vs. excipient gel alone is very uncertain.	(30)
Clinical attachment level (CAL) (90 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Serious	Undetected	⊕⊕⊕⊕ VERY LOW	vs. CI: MD 0.34 mm lower with HA (95% CI 1.01 lower to 0.33 higher), NS vs. C2: MD 0.16 mm higher with HA (95% CI 0.41 lower to 0.73 higher), NS	No important difference detected in clinical attachment level between HA gel and either control at 90 days.	(30)
Marginal bone loss (MBL) (90 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Serious	Undetected	⊕⊕⊕⊕ VERY LOW	vs. CI: MD 0.27 mm lower with HA (95% CI 1.19 lower to 0.65 higher), NS vs. C2: MD 0.04 mm lower with HA (95% CI 0.70 lower to 0.62 higher), NS	Marginal bone levels were radiographically stable in all groups; no important difference detected over 90 days.	(30)
Crevicular IL-1β, implants with baseline PPD ≥5 mm-HA vs. no treatment (45 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	61 patients (1 RCT)	Serious	N/A (single trial)	Serious	Serious	Undetected	⊕⊕⊕⊕ VERY LOW	MD 51 pg/ml lower with HA (95% CI 3 to 98 pg/ml lower)-significant only in this deeper-pocket subgroup	In implants with deeper pockets (≥5 mm), HA gel may reduce crevicular IL-1β more than no treatment.	(30)
Submucosal microbial alpha-diversity (InvSimpson/Shannon), advanced sites-HA vs. excipient/no treatment (45 days)	0.8% High-molecular-weight hyaluronic acid (HMW-HA) gel vs. excipient gel/no treatment (peri-implantitis)	-18-19 pts/arm (1 RCT companion study)	Serious	N/A (single trial)	Serious	Very serious	Undetected	⊕⊕⊕⊕ VERY LOW	Descriptive only (median [IQR], no between-group CI): InvSimpson fell 10.16→4.99 with HA and rose 4.18→5.90 with no treatment in advanced sites (Stratum 3); excipient-gel group showed no significant change (6.42→6.20)	May shift the submucosal microbiome toward a less pathogenic profile in advanced peri-implantitis, but this is an exploratory companion analysis of a small subgroup with no formal between-group test; certainty very low.	(31)

RCT, randomised controlled trial; mo, months; MD, mean difference; pp, percentage points; CI, confidence interval; NS, not significant. GRADE certainty: ⊕⊕⊕⊕ HIGH; ⊕⊕⊕⊕ MODERATE; ⊕⊕⊕⊕ LOW; ⊕⊕⊕⊕ VERY LOW. Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31) are companion publications from the same RCT (NCT03157193) and do not represent independent trial populations; their outcomes are treated as a single body of evidence throughout this table.

Interpretation of main findings. Across the included studies, mechanical debridement with topical adjuncts was consistently associated with improvements from baseline; however, the extent to which these enhancements were attributable to the adjuncts varied. Scribante *et al* (32) found that a 15% ozonated sunflower oil hydrogel produced more rapid and greater improvements in bleeding on probing, bleeding scores and suppuration than a 1% chlorhexidine gel over a period of 24 months. The differences between groups were statistically significant from 12 to 24 months. Plaque index and marginal mucosal condition improved in both study arms, with between-group differences emerging only late in follow-up and not sustained at 24 months, whereas probing depth and marginal bone level did not differ significantly between groups (32). This observation aligns with the findings of Butera *et al* (33), who observed significant differences between groups favouring the ozonated gel for plaque index, bleeding on probing and bleeding score by 3 months. Probing depth, suppuration and marginal mucosal condition improved in both groups, with no significant between-group differences at any assessed time point (33). The anti-inflammatory effects of ozone-based formulations may reflect the biological activity of the triatomic oxygen molecule, which exerts anti-microbial, anti-inflammatory and immunomodulatory effects by disrupting microbial cell walls, causing oxidative damage to nucleic acids and proteins and inactivating viruses. HA also demonstrated clinically significant benefits in peri-implantitis. Sánchez-Fernández *et al* (30) found that topical 0.8% HMW-HA produced a significantly greater decrease in PPD compared with excipient gel and no-treatment controls at 45 and 90 days. For implants with probing depths ≥ 5 mm, crevicular IL-1 β levels were significantly lower in the HA group, providing biochemical evidence of its anti-inflammatory effect. Bleeding on probing exhibited a similar, non-significant trend favouring HA, and no significant differences were noted in clinical attachment level, marginal bone level or crevicular TNF- α between the groups (30). The microbiome analysis of the same cohort by Soriano-Lerma *et al* (31) revealed that HA lowered peri-implantitis-related organisms, particularly early colonisers, and reduced microbial alpha diversity in advanced cases (31). Atorvastatin gel produced statistically significant between-group improvements in clinical attachment level and pain on probing over 3 months; however, bleeding on probing was significantly higher (worse) with atorvastatin than with the placebo at 3 months, despite an initial within-group reduction in both study arms. Probing depth improved within both groups but did not differ significantly between groups ($P=0.25$), extending the evidence for statins from chronic periodontitis to peri-implant conditions (35). Chlorhexidine gel performed comparably to, or worse than, alternative therapies: Storelli *et al* (34) identified no significant difference between 1% chlorhexidine and a bio-adhesive antiseptic gel in the modified bleeding index or plaque index, with similar 'healing' rates (~65-67%). However, the chlorhexidine group developed tooth and prosthetic staining absent in the comparator group (34).

Biological plausibility and mechanisms of action. The differential efficacy of these adjuncts can be explained by their mechanisms. Ozonated hydrogels function via multiple anti-microbial pathways: The oxidation of polyunsaturated

fatty acids in bacterial membranes triggers lipid peroxidation and membrane disruption. By contrast, the oxidation of sulphhydryl groups and amino acids inactivates bacterial proteins and nucleic acids, and Gram-negative pathogens are particularly susceptible. Beyond direct anti-microbial action, ozone modulates immunity via reactive oxygen species signalling, which can recruit phagocytes and promote the resolution of inflammation (32,33). HA restores homeostasis of the extracellular matrix. HMW-HA provides structural support and hydration, binds to cluster of differentiation 44 and the receptor for hyaluronan-mediated motility, and activates the phosphoinositide 3-kinase/protein kinase B and extracellular signal-regulated kinase cascades that promote fibroblast survival and matrix synthesis. HMW-HA also antagonises pro-inflammatory signalling triggered by low-molecular-weight HA fragments (which engage Toll-like receptors 2/4 to amplify TNF- α and IL-6) and supports tissue inhibitors of metalloproteinases, helping to restore the matrix metalloproteinase/tissue inhibitor of metalloproteinase balance (30,31). Atorvastatin exerts pleiotropic effects by inhibiting the mevalonate pathway, thereby reducing the geranylgeranylation of Ras-homologous guanosine triphosphatases and attenuating NF- κ B and MAPK signalling. Moreover, it enhances bone morphogenetic protein (BMP)-2 and BMP-4 signalling via Smad-dependent pathways, promoting osteoblastic differentiation, while antagonising receptor activator of NF- κ B ligand-mediated osteoclastogenesis (35). By contrast, chlorhexidine functions purely via an anti-microbial mechanism (cationic disruption of bacterial membranes) and neither supports tissue repair nor modulates the inflammatory response. These constraints, together with substantivity-related staining and a lack of regenerative potential, may help explain the comparatively limited long-term performance of chlorhexidine relative to multifunctional agents.

Implant systems and surface characteristics. Implant type and surface topography were not reported in the majority of trials. This is a notable limitation as surface roughness and chemistry influence biofilm retention, the accessibility of decontamination and the response of peri-implant tissues to adjunctive agents. The inability to relate outcomes to implant-surface characteristics limits external validity and complicates cross-study comparison; future trials should report implant systems and surface properties so that their interaction with adjunctive therapy can be evaluated.

Sources of heterogeneity and their implications. The six reports varied significantly in terms of hydrogel composition (ozonated sunflower-oil hydrogel, atorvastatin gel, a bio-adhesive antiseptic gel and HMW-HA), application protocols (single in-office application vs. combined in-office plus once- to thrice-daily home use), treatment durations (14 days vs. a single 45-day regimen) and follow-up periods (45 days to 24 months). The reports covered two diagnostically distinct groups: Peri-implant mucositis [Scribante *et al* (32), Butera *et al* (33), Khorramdel *et al* (35) and Storelli *et al* (34)] and peri-implantitis with radiographic bone loss [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)].

Heterogeneity by hydrogel type and mechanism of action. The four test formulations function via distinct pathways

that only partially overlap. Ozonated sunflower-oil hydrogel [Scribante *et al* (32) and Butera *et al* (33)], is predominantly anti-microbial, disrupting bacterial membranes, nucleic acids and proteins, with a secondary anti-inflammatory effect via reactive oxygen species signalling. Atorvastatin gel [Khorramdel *et al* (35)] instead functions via a host-directed pathway, inhibiting the mevalonate pathway to attenuate NF- κ B/MAPK signalling and promote osteoblastic differentiation, without direct anti-microbial activity (35). The bio-adhesive antiseptic gel [Storelli *et al* (34)] integrates a cationic antiseptic (cetylpyridinium chloride and triclosan) with HA and re-epithelializing agents, such as allantoin, bisabolol and vitamin E. Mechanistically, it aligns more closely with chlorhexidine, its comparator, than with the other three agents (34). HMW-HA [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)] is immunomodulatory and tissue-reparative, suppressing pro-inflammatory signalling triggered by HMW-HA fragments and supporting extracellular matrix homeostasis. As these agents function via different, non-equivalent mechanisms, the pooled references to 'hydrogels' in the Abstract and conclusion paragraph below summarise directionally similar, yet mechanistically distinct interventions rather than a shared class effect.

Heterogeneity by application protocol. The dosing intensity varied significantly, ranging from a single subgingival injection with no repeat [Khorramdel *et al* (35)] to a one-time in-office application followed by patient-applied gel three times daily for 45 days [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)]. Other protocols included daily home use for 14 days following each office visit [Scribante *et al* (32) and Butera *et al* (33)] and continuous twice-daily home use throughout the follow-up period [Storelli *et al* (34)]. This variation in cumulative exposure may partly explain the observed heterogeneity in effect size: The two trials with the most sustained, repeated dosing (the ozonated-gel trials) displayed the most consistent inflammatory benefit, whereas the single-application atorvastatin. The HA trials do not follow a straightforward dose-response pattern: despite a comparably sustained regimen (thrice-daily home use for 45 days), their benefit remained confined to a single outcome (probing depth), rather than extending to the broader inflammatory improvement observed with the ozonated gel. As the formulation and dosing schedule were fully confounded, with each agent tested using only one protocol, this contribution cannot be separated from that of the active agent itself and is offered as a hypothesis for future head-to-head or dose-ranging trials.

Heterogeneity by disease severity. Baseline severity varied to a greater extent than the simple mucositis/peri-implantitis division suggests: The criteria in the study by Khorramdel *et al* (35) included severe peri-implant mucositis or mild peri-implantitis with up to 2 mm crestal bone loss, blurring the distinction between the two conditions. In the peri-implantitis group, Sánchez-Fernández *et al* (30) observed a significant decrease in crevicular IL-1 β with HA only in implants with baseline probing depths ≥ 5 mm. Similarly, the microbiome analysis by Soriano-Lerma *et al* (31) found that the impact of HA on pathogen abundance and diversity was concentrated in the most dysbiotic baseline group. Although these findings are based on post hoc sub-groups within a single trial, they suggest that the benefits of adjunctive hydrogel

depend on baseline severity or dysbiosis level, rather than being uniform; however, this hypothesis could not be tested in other included trials because none of the mucositis studies stratified participants by baseline severity.

Collectively, these three axes of heterogeneity mean that the observed effects cannot be attributed to a generic hydrogel effect. Each finding should be interpreted as specific to its formulation, dosing regimen and population, the basis for the more qualified, agent-specific wording used above and in the conclusion paragraph below. As formulation, protocol and severity are confounded in datasets with only one or two trials per agent, a formal quantitative sub-group analysis or meta-regression was not statistically feasible; the conceptual sub-grouping above is intended as a starting point for future trials, not a substitute for one. This heterogeneity, together with reliance on single small trials for most comparisons, is the principal reason the certainty of the evidence did not exceed moderate for any outcome.

Limitations. Several limitations should be considered. First, substantial heterogeneity in case definitions, outcome measures and follow-up durations precluded a meta-analysis and limited comparative conclusions. The present systematic review combines two diagnostically distinct conditions, peri-implant mucositis and peri-implantitis, which differ in diagnostic criteria, primary outcomes and treatment goals; only one trial cohort focused on peri-implantitis (30,31). This 'transdiagnostic' combination, necessitated by the scarcity of eligible peri-implantitis RCTs, means the findings for the two conditions should be treated as separate bodies of evidence rather than a single conclusion; future reviews should use independent PICO (population, intervention, comparator and outcome) frameworks as the peri-implantitis literature grows. Second, two of the six included reports [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)] are based on a single cohort; thus, the body of evidence comprises five independent trials rather than six. Third, a high proportion of full texts (8 of 28 sought) could not be retrieved, introducing potential selection bias and limiting completeness, despite attempts to contact authors and to obtain articles via institutional and interlibrary access. The direction of this non-retrieval bias is uncertain: Some reports not retrieved may be null or negative findings from lower-visibility sources, which would inflate the apparent benefit reported herein; others may simply reflect access barriers unrelated to the outcome. As heterogeneity precluded a meta-analysis, a formal sensitivity analysis was not feasible. This bias is therefore acknowledged qualitatively, and its magnitude remains unquantifiable. Fourth, several trials had small samples [notably Storelli *et al* (34), with 18 participants analysed], reducing the statistical power. Fifth, split-mouth designs, although controlling for inter-individual variability, carry a risk of carry-over effects, and blinding was not feasible in all trials, exacerbating the risk of performance and detection bias. Sixth, the exclusion of smokers from the majority of trials limits applicability to this high-risk group, and the short follow-up in several studies [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)] (45-90 days) hinders the assessment of long-term stability, recurrence and implant survival. Finally, the emphasis on surrogate clinical measures overshadowed patient-centred outcomes. Future studies are warranted to

integrate patient-reported outcome measures with clinical and radiographic assessments.

Directions for future research. Well-designed, multi-centre RCTs with standardised outcome measures and extended follow-up are required to confirm the comparative efficacy of adjunctive hydrogels. External validity would be enhanced by including high-risk patients (e.g., those with diabetes or a history of smoking). Direct comparisons of ozone-based formulations with emerging adjuncts, such as probiotics, photodynamic therapy or peptide biomodulators, would clarify their relative utility. Incorporating microbiological and biochemical assessments could clarify mechanisms and identify predictive biomarkers. Standardised application protocols (concentration, frequency and duration) would facilitate cross-study comparisons and clinical translation. Cost-effectiveness analyses are also needed to inform policy and resource allocation.

Clinical implications. For the maintenance of peri-implant mucositis, ozonated oil-based hydrogels may represent a reasonable alternative to chlorhexidine, providing comparable efficacy without staining or taste alteration. HA gel may be particularly useful for peri-implantitis with moderate-to-deep pockets, given its antimicrobial and anti-inflammatory properties, although this is based on outcome-level evidence from a single 61-participant trial cohort reported in two publications [Sánchez-Fernández *et al* (30) and Soriano-Lerma *et al* (31)], not from multiple independent studies. Combining patient-administered home care with professional in-office application may improve outcomes and compliance over longer follow-up. In the 24-month ozone trial, no peri-implantitis progression and stable marginal bone levels were observed, underscoring the value of prompt, effective treatment in arresting peri-implant mucositis, consistent with the consensus that peri-implant mucositis is reversible when identified early and managed with appropriate non-surgical therapy. As the supporting evidence is of very low to moderate certainty, these implications should be regarded as provisional.

Adjunctive hydrogel therapies appear to offer promising but modest and inconsistent benefits in the non-surgical management of peri-implant mucositis and early peri-implantitis. Probing-depth reductions were generally small and variable, whereas ozonated hydrogels and high-molecular-weight HA were more consistently associated with improvements in soft-tissue inflammation parameters, and atorvastatin gel was associated with improvements in clinical attachment level and pain on probing, but not bleeding on probing, compared with mechanical debridement alone or other adjuncts. When appraised using GRADE, the certainty of evidence ranged from very low to moderate, downgraded for risk of bias, inconsistency, indirectness, and imprecision depending on the outcome. Heterogeneous formulations, protocols, and follow-up durations highlight the need for standardised, longer-term RCTs to confirm the durability of effects and to inform evidence-based guidelines before targeted clinical recommendations can be made.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BG and RC conceptualised the study and were involved in the formal analysis, and in the writing of the original draft of the manuscript. BG and NS were involved in the study methodology. NS was involved in validation of the risk-of-bias and GRADE certainty assessments. BG, RC, NS and SS were involved in data acquisition, and in the writing, review and editing of the manuscript. BG and NS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (OpenAI) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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