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Effectiveness of Biologically Active Agents and Biomaterials for the Management of Peri-Implant Soft Tissue Defects: A Systematic Review

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Abstract

Peri-implant soft tissue deficiencies may affect the esthetic appearance of implant-supported restorations. Autogenous soft tissue grafting remains established, although donor-site morbidity has encouraged interest in less invasive approaches. This systematic review evaluated the clinical effectiveness of biologically active agents and biomaterials for managing peri-implant soft tissue deficiencies and assessed their impact on clinical, esthetic, and patient-reported outcomes. We searched multiple electronic databases. Eligible studies evaluated biologically active agents or biomaterials for peri-implant soft tissue deficiencies. Two reviewers independently screened studies, extracted data, and assessed risk of bias. Due to substantial heterogeneity in interventions, comparators, outcomes, and follow-up periods, a narrative synthesis was performed on the five eligible studies. Five studies met the eligibility criteria. The findings indicated that free gingival grafts (FGG) remain the most predictable intervention for increasing keratinized mucosa width (KMW). However, injectable platelet-rich fibrin (i-PRF) and hyaluronic acid (HA), especially when combined with microneedling, significantly improved peri-implant mucosal thickness (PIMT) and modified the phenotype. Furthermore, combining FGG with xenogeneic collagen matrices (XCM) provided clinical gains comparable to conventional FGG while significantly reducing postoperative morbidity and enhancing esthetic outcomes. Biologically active agents and biomaterials may improve peri-implant soft tissue outcomes. However, evidence remains limited and heterogeneous, and these approaches cannot currently replace autogenous soft tissue grafting.

Categories: Dentistry
Keywords: biologically active agents, growth factors, hyaluronic acid, keratinized mucosa, peri-implant soft tissue defects, platelet-rich fibrin

Introduction And Background

Tooth replacement restores masticatory function, esthetics, and quality of life after tooth loss [1]. The principal options include removable partial dentures (RPDs), fixed partial dentures (FPDs), dental implants, and resin-bonded restorations, each with distinct advantages and limitations [1].

Dental implant success depends on several factors, including alveolar bone quantity and quality, the patient's systemic health, oral hygiene practices, and the biomechanical load on the implant. Advances in dental implant design, surface modification, and surgical techniques have contributed to high survival rates, with long-term studies reporting success rates exceeding 90% over 10 years [2]. A recent 2024 meta-analysis reported high survival rates for dental implants after 20 years, with four out of five implants surviving despite the multifactorial nature of implant failure [3]. A significant difference in survival rates between 10 and 20 years indicates that dental implant therapy does not end after the initial surgery but requires lifelong follow-up care.

However, implant therapy carries risks and complications. Complications such as peri-mucositis, peri-implantitis, and mechanical failures (e.g., screw loosening or fracture) must be carefully managed. Furthermore, selecting appropriate cases and adopting a multidisciplinary approach are essential for achieving optimal outcomes [4-6]. One of the most reported complications is a peri-implant soft tissue defect. This may occur as a result of the host responding to implant diseases (peri-mucositis or peri-implantitis) or due to anatomical and local factors such as trauma to the soft tissue and loss of supporting structures surrounding the dental implant (e.g., frenal pull or thin gingival phenotype).

Peri-implant soft tissue defects (PSTDs) are a common complication following dental implant placement, frequently resulting in both esthetic concerns and functional impairments [7,8]. Various surgical techniques have been utilized to correct these defects. These include sole mucogingival intervention [9-11]; combined prosthetic and mucogingival interventions [12,13]; dental implant submergence [14,15] followed by vertical soft tissue augmentation over the submerged dental implant using connective tissue grafts to restore optimal vertical peri-implant soft tissue height [16]; and the use of growth factors [17]. Regardless of the

interventions, many factors can influence the outcome of peri-implant soft tissue defect management (e.g., implant angulation and underlying bone and mucosal morphology) [18].

Peri-implant soft tissue integrity plays a critical role in maintaining long-term implant health, preventing inflammation, and achieving predictable esthetic outcomes [19]. Conventional management of peri-implant soft tissue deficiencies includes autogenous grafts (connective tissue grafts (CTG) or free gingival grafts (FGG)), collagen-based matrices, and combined surgical-prosthetic approaches [20]. Although autogenous grafts remain highly predictable, their use may be associated with donor-site morbidity, increased surgical time, postoperative discomfort, and limited patient acceptance. In recent years, biologically active agents and biomaterials such as hyaluronic acid (HA), platelet-rich fibrin (PRF), platelet-rich plasma (PRP), enamel matrix derivatives (EMD), concentrated growth factors (CGF), and recombinant growth factors have emerged as potential alternatives or adjuncts due to their ability to stimulate wound healing, angiogenesis, and soft tissue regeneration [20,21].

Despite growing clinical interest, the evidence supporting the effectiveness of these biomolecules in managing PSTD remains inconsistent and fragmented. Existing studies vary in design, use diverse biomolecule preparation protocols, and assess a wide range of clinical outcomes, making it difficult to establish clear clinical guidelines. Furthermore, most available data are limited by small sample sizes, short follow-up periods, and a lack of standardised reporting, leaving significant uncertainty regarding the long-term stability and comparative effectiveness of these biologic approaches relative to conventional grafting techniques.

Given these limitations, a systematic review is needed to critically appraise and synthesise evidence on biologically active agents and biomaterials for peri-implant soft tissue regeneration. Such a review will help clarify the potential benefits, limitations, and clinical applicability, while identifying key research gaps to guide future investigations and support the development of evidence-based therapeutic protocols.

To date, no study has conclusively examined or reviewed the effects of varieties of biologically active agents and biomaterials such as HA, PRF, PRP, EMD, CGF, and recombinant growth factors in relation to autogenous grafts in managing PSTDs. Available evidence has examined the effects of certain biologically active agents and biomaterials; however, a comprehensive evaluation across a broader range of interventions remains lacking. This systematic review aims to evaluate published articles on the efficacy and benefits of these materials in managing peri-implant soft tissue defects.

Review

Methodology

Standardized Criteria and Study Type

This systematic review was developed and designed according to the Cochrane Collaboration standard protocol and criteria [22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23].

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) before screening and data extraction began (registration number: CRD420251266413). The protocol is available at: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251266413.

The study was exempted from review by the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia, and this systematic review is registered under NMRR ID-26-00090-N2B.

Focused Questions

This study has four focused questions. First, do biologically active agents and biomaterials improve peri-implant soft tissue outcomes compared to conventional treatment? Second, which biologically active agents, biomaterials, and application protocols are most effective for peri-implant soft tissue augmentation? Third, are improvements from biologically active agents and biomaterials maintained over time, and how do they compare with autogenous grafts such as free gingival grafts and connective tissue grafts? Lastly, do biologically active agents and biomaterials reduce morbidity, improve esthetics, and enhance patient satisfaction compared with conventional approaches?

Study Population and Eligibility Criteria

We selected studies according to predefined inclusion and exclusion criteria developed using the PICOS (Population, Intervention, Comparator, Outcomes, and Study design) framework (Table *1*). Eligible studies involved adult participants who received dental implants and presented with PSTD (e.g., reduced keratinized mucosa, thin mucosa, peri-implant recession).

Criterion	Inclusion criteria	Exclusion criteria
Population	Studies involving human adults diagnosed with PSTDs (e.g., reduced keratinized mucosa, thin mucosa, peri-implant recession)	Animal studies or in vitro studies and studies not involving PSTDs
Intervention	Participants received management of PSTDs using biologically active agents and biomaterials (e.g., HA, PRF, PRP, PDGF, EMD, biomolecule-enriched scaffolds) either through non-surgical or surgical modalities, with a minimum of six weeks to six months follow-up	Studies not evaluating the management of PSTDs using biologically active agents and biomaterials
Comparator	Participants received management of PSTDs using conventional grafting (CTG, FGG, collagen matrices) or no intervention	Comparator protocols insufficiently described for interpretation or studies
Outcome	Clinical (effect on keratinized mucosa width, mucosal thickness, soft tissue stability), procedural outcomes (healing rate, tissue integration), and patient-reported outcomes (pain, morbidity, recovery time, esthetic satisfaction, quality of life measures)	Studies insufficiently described for interpretation on outcomes
Study design	Randomized controlled trials, non-randomized comparative studies, and prospective single-arm interventional studies with eligible clinical outcomes and follow-up	Case reports, retrospective case series, non-interventional observational studies, animal or in-vitro studies and review articles
Publication formats	Full-text peer-reviewed articles	Grey literature without peer review
Language	English or translated into the English language	Studies published in languages other than English
Publication period	Studies available and published from January 2016- June 2026	Studies published before and after January 2016- June 2026

TABLE 1: Inclusion and exclusion criteria based on the PICOS framework

CTG: connective tissue graft; EMD: enamel matrix derivative; FGG: free gingival graft; HA: hyaluronic acid; PDGF: platelet-derived growth factor; PRF: platelet-rich fibrin; PRP: platelet-rich plasma; PSTDs: peri-implant soft tissue defects; PICOS: Population, Intervention, Comparator, Outcomes, and Study design

Type of Outcome Measures

The primary outcomes were gain in keratinized mucosal width (KMW; mm) and change in peri-implant mucosal thickness (PIMT; mm). Secondary outcomes included esthetic indices (pink or white esthetic score), patient-reported pain and morbidity, implant survival, and adverse events related to biologically active agents and biomaterials use.

Search Methods for Study Identification

This study used Web of Science (WOS), The Cochrane Library, MEDLINE (PubMed), Scopus, and Europe PMC for electronic searches. We searched for articles published between January 2016 and June 2026. We used a Boolean search strategy, combining concepts and subject headings for each database search (Appendix 1). We did not filter the search by language. However, we restricted the search to January 2016 to June 2026 and to randomized or non-randomized clinical trials.

Reference lists of selected articles and related review articles were manually searched as a complement to the database electronic search. We searched key related journals, including *Journal of Periodontal Research*, *Journal of Periodontology*, *Clinical Implant Dentistry*, *Clinical Oral Implant Research*, and *Journal of Clinical Periodontology*, from January 2016 to June 2026. We searched for clinical trials in progress through the online database https://clinicaltrials.gov. No partial gray literature search was performed.

Data Collection and Analysis

We imported all records identified through the electronic database search, hand-searching, and other sources into Rayyan software (https://www.rayyan.ai) for study management. We identified and removed duplicate records before screening. The eligibility of studies was assessed through a two-stage screening process by two reviewers (SNA and NAMY). First, titles and abstracts were independently screened against the predefined eligibility criteria. When the title and abstract did not provide sufficient information to

determine eligibility, we retrieved and evaluated the full-text article. Full-text articles of potentially eligible studies were then retrieved and independently assessed for inclusion. We excluded studies that did not meet the eligibility criteria and documented the reasons for exclusion at the full-text stage. Reviewers resolved disagreements through discussion; when consensus could not be reached, a third reviewer (MAJ) was consulted. The study selection process is presented using a PRISMA 2020 flow diagram [23].

Data extraction was performed by two reviewers (SNA and NAMY) using a standardized data extraction form specifically developed for this systematic review. The form was subsequently refined during a second review process to incorporate additional study characteristics and primary and secondary outcome measures. All extracted data and completed data forms were independently reviewed by the third reviewer (MAJ) for accuracy and completeness. We held consensus discussions throughout study selection, data extraction, and data verification until we reached agreement. All reviewers collaborated to consolidate and analyze the extracted data for this review.

We recorded study characteristics in the data extraction form. Where necessary, we contacted the corresponding authors of included studies via email to clarify missing data, methodological details, or reported outcomes.

The risk of bias and methodological quality of the included studies were independently assessed by two reviewers (SNA and NAMY) using the Cochrane Risk of Bias 2 (RoB 2) tool [24] and the National Heart, Lung, and Blood Institute (NHLBI) tool [25]. We applied the Cochrane RoB 2 tool to randomized clinical trials (RCTs) to evaluate potential biases arising from randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting of results. We rated each domain as ‘low risk’, ‘some concern’, or ‘high risk’, and assigned an overall rating [24]. We used the NHLBI tool to assess risk of bias in non-randomized studies of interventions. Depending on the research design, the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group was used [25]. Each domain was rated as ‘yes’, ‘no’, ‘not applicable’, or ‘not reported’. The overall rating of each study could be ‘good’, ‘fair’, or ‘poor’ [25].

Reviewers classified each domain as low risk of bias, some concerns, or high risk of bias. Reviewers resolved disagreements through discussion, with adjudication by a third reviewer (MAJ) when consensus could not be reached. For study screening, inter-rater agreement between the two reviewers was Cohen’s Kappa (κ = 0.85). For risk-of-bias assessment, the agreement coefficient was (κ = 0.95). These values represent agreement between the reviewers’ independent assessments before consensus or adjudication.

Data Synthesis

We conducted a narrative synthesis to summarise the included studies’ findings. Studies were grouped by the intervention evaluated, the comparator used, and the reported clinical outcomes. We grouped interventions by category, including platelet concentrates and other biologically active agents, as well as biomaterials used for peri-implant soft-tissue augmentation. Outcomes were synthesized separately where data were available, including keratinized mucosa width, soft-tissue thickness, peri-implant soft-tissue recession, and patient-reported outcomes.

For each study, we extracted and summarised the reported outcome measurements using the effect measures provided in the original publication, including mean values, changes from baseline, between-group differences, and P values, where available. We compared findings descriptively by considering the direction and magnitude of reported effects and the statistical significance of between-group comparisons. Statistical significance was interpreted in the context of the specific outcome and comparison reported in each study; numerical differences alone were not considered evidence of a statistically significant treatment effect.

We did not undertake a meta-analysis because differences in intervention protocols, comparator groups, outcome definitions, measurement methods, and follow-up periods limited the clinical and methodological comparability of the studies. We presented the findings in summary tables and synthesized them narratively, accounting for differences in study design and methodological quality. The synthesis was reported with reference to the Synthesis Without Meta-analysis (SwiM) reporting guideline [26].

Assessing the Certainty of the Evidence

The certainty of evidence for each clinical outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [27]. Certainty was considered separately for KMW, PIMT, papillary and recession-related outcomes, peri-implant clinical parameters, patient-reported outcomes and postoperative morbidity, and esthetic outcomes.

The GRADE framework evaluates five domains that may reduce certainty: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Randomized controlled trials initially provide high-certainty evidence, whereas non-randomized studies begin at a lower level of certainty. Evidence was downgraded by one level for serious concerns or by two levels for very serious concerns within an applicable domain. We

determined overall certainty for each outcome by considering the combined impact of these domains, rather than counting studies that reported statistically significant findings.

Risk of bias was assessed using the methodological quality assessments conducted for the included studies. Inconsistency was considered in relation to the direction and magnitude of treatment effects across studies addressing comparable clinical questions. We assessed indirectness based on how relevant the study populations, interventions, comparators, and outcomes were to the review question. We evaluated imprecision by considering sample sizes, the precision of effect estimates and confidence intervals (where available), and the extent to which the evidence could support clinically meaningful conclusions. We considered publication bias given the number of studies and the feasibility of assessing small-study effects.

We classified the certainty of evidence as high, moderate, low, or very low. High certainty indicates strong confidence that the true effect is close to the estimated effect; moderate certainty indicates reasonable confidence; low certainty indicates limited confidence; and very low certainty indicates very little confidence in the estimated effect. Because the included studies differed substantially in their interventions, comparators, outcome measurements, and follow-up periods, the findings were synthesized narratively without calculating pooled effect estimates. When comparable effect estimates and confidence intervals were unavailable, we considered this limitation when interpreting imprecision and did not infer numerical effect estimates from statistical significance alone.

Results

Study Selection

We identified 149 records from five databases, plus two additional records through hand search. After removing duplicates, we screened 100 records, assessed 31 for full-text review, and included five in this systematic review (Figure *1*).

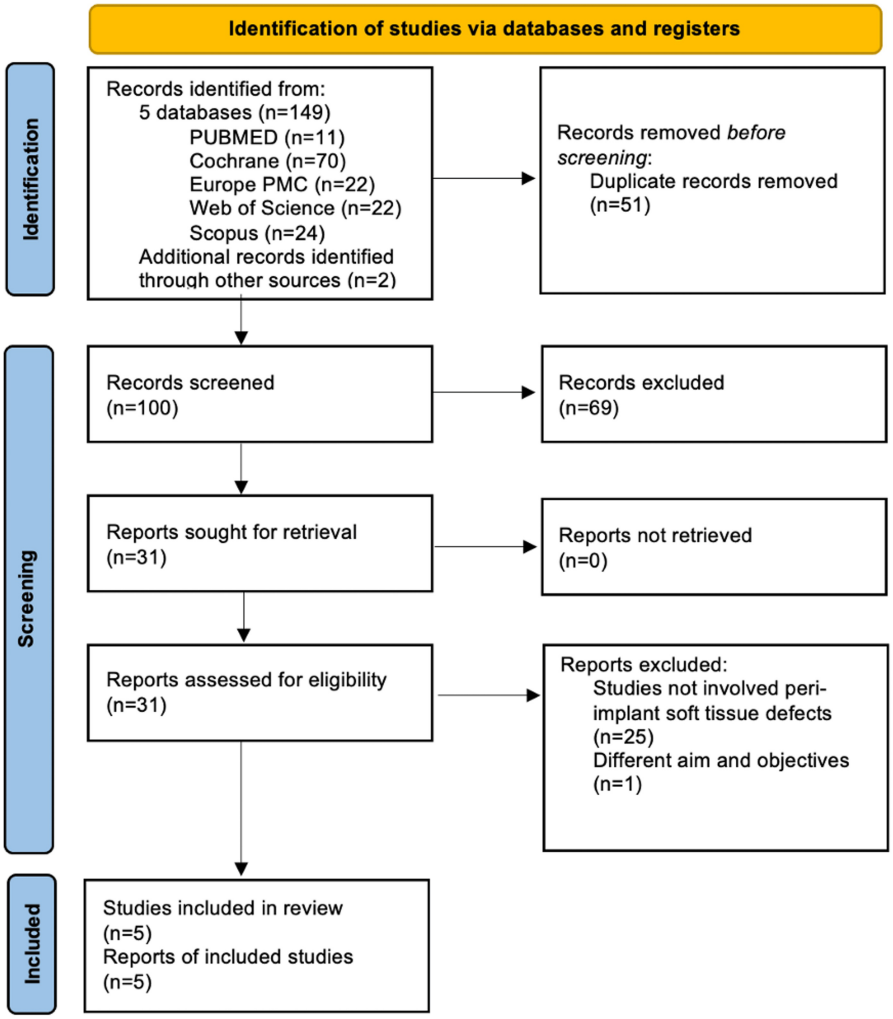


FIGURE 1: PRISMA flow diagram showing the study selection process

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

This review included five studies published between January 2016 and June 2026. Of the five included studies, four were randomized controlled trials: three parallel-group [28-30] and one split-mouth design [31], and one was a non-randomized clinical study [32] (Table *2*). The studies were conducted in Denmark (n = 1), Belgium (n = 1), and India (n = 3), with sample sizes ranging from eight to 65 participants and follow-up periods between six weeks and six months. The interventions addressed peri-implant soft tissue deficiencies, including inadequate keratinized mucosa, deficient interproximal papillae, and thin peri-implant soft tissue phenotypes.

Study	Country	Study design	Sample size	Population/defect type	Intervention	Comparator	Follow-up	Primary outcomes	Secondary outcomes	Main findings
Bertl et al., 2017 [28]	Denmark	Parallel RCT	22 patients	Deficient interproximal papilla adjacent to implant-supported crowns in anterior maxilla	HA injections (2 sessions)	Saline injections	6 months	PT-CP distance, MPIS, black triangle area, mucosal volume changes	VAS esthetic score, pain, radiographic bone level	No significant difference between HA and saline. HA failed to provide clinically relevant papilla augmentation.
Temmerman et al., 2018 [31]	Belgium	Split-mouth RCT	8 patients	< 2 mm keratinized mucosa around bilateral mandibular implants	L-PRF membranes	FGG	6 weeks	Gain in KMW	Postoperative pain, surgical time	Both groups increased KMW. FGG produced greater gain (+1.3 mm), whereas L-PRF reduced surgical time and morbidity.
Farooqui et al., 2023 [29]	India	Parallel RCT	30 patients	Minimal peri-implant KM ≤ 1 mm	FGG strips + XCM	FGG	6 months	Gain in KMW	Better esthetic outcomes and lower morbidity in test group compared to control group	After 1 month, both groups showed statistically significant gain in KMW. When the gain was compared between the two groups, the difference was not statistically significant. Better esthetic outcomes and lower morbidity were reported in the test group compared to the control group, and this difference was statistically significant.
Bawankar et al., 2024 [30]	India	Parallel RCT	65 patients	Thin peri-implant phenotype with keratinized mucosa < 1 mm	MN + injectable HA	MN alone	6 months	PIMT, KMW, PRH, IPW	PI, GI, SBI, CAL, PROMs	HA + MN significantly improved PIMT, KMW, and papillary fill compared with MN alone.
Chittabathina et al., 2026 [32]	India	Non-RCT	15 dental implants	Thin PIMT	i-PRF + MN	No control	6 months	PIMT and KMW	PES and VAS	i-PRF + MN increase PIMT in patients with thin peri-implant phenotypes and enhance KMW dimensions

TABLE 2: Characteristics of included studies

RCT: randomized clinical trial; HA: hyaluronic acid; MPIS: modified papilla index score; KMW: keratinized mucosa width; PIMT: peri-implant mucosal thickness; FGG: free gingival graft; L-PRF: leukocyte and platelet rich fibrin; PRH: papillary recession height; IPW: interproximal width; MN: microneedling; i-PRF: injectable platelet rich fibrin; PROMs: patient-reported outcome measures; SBI: Sulcus Bleeding Index; GI: Gingival Index; PI: Plaque Index; XCM: xenogeneic collagen matrix; PES: Pink Esthetic Score

Intervention Characteristics

The included studies evaluated several biomaterials and biologically active agents, including HA, leukocyte- and platelet-rich fibrin (L-PRF), i-PRF, and FGG, either alone or combined with an XCM. Intervention protocols varied considerably, including preparation methods, application techniques, and treatment frequency. HA was administered as a single [30] or repeated injection [28]; L-PRF [31] and FGG [29] were applied during a single surgical procedure, whereas i-PRF was delivered through three injection sessions at 10-day intervals [32] (Table *3*).

Study	Biomaterial/biological active agent	Concentration/preparation	Application protocol	Number of applications
Bertl et al., 2017 [28]	HA (Hyadent Barrier Gel)	16 mg cross-linked Na-hyaluronate + 2 mg Na-hyaluronate	3-step injection technique	2 injections (4 weeks apart)
Temmerman et al., 2018 [31]	L-PRF	4 × 9 mL blood tubes centrifuged at 2700 rpm for 12 min	Membranes sutured over recipient site	Single surgery
Farooqui et al., 2023 [29]	FGG	FGG (2 mm wide and 1-1.5 mm thick) – harvested from the palate	FGG and strip placed apically onto the recipient bed and stabilized using sutures	Single surgery
Bawankar et al., 2024 [30]	Cross-linked injectable HA	20 mg/mL; particle size 400 µm	Injection after MN	Single application
Chittabathina et al., 2026 [32]	i-PRF + MN	10 ml blood added to i-PRF tube centrifuged at 700 rpm for 3 min	Injection through peri-implant sulcus, keratinized mucosa	3 times with a 10-day gap between visits

TABLE 3: Intervention characteristics

HA: hyaluronic acid; FGG: free gingival graft; L-PRF: leukocyte and platelet rich fibrin; MN: microneedling; i-PRF: injectable platelet rich fibrin

Clinical Outcomes

Clinical outcomes varied among the included studies and primarily comprised KMW, PIMT, papillary and recession-related parameters, and peri-implant clinical indices. The included studies evaluated different interventions, comparators, clinical indications, and outcome measures; therefore, we synthesized the findings narratively rather than quantitatively.

KMW was the most frequently assessed clinical outcome. Both L-PRF and FGG increased keratinized tissue; however, FGG showed significantly greater tissue gain than L-PRF (mean difference, 1.3 mm). Unfortunately, the study showed shrinkage of the augmented sites, measured by comparing the buccal width of the KM at the postoperative visit and at six weeks later, which was slightly higher at the test site (32.1%) than at the control side (23.6%). However, this difference was not statistically significant (P>.05) [31]. Similarly, improvements in KMW were achieved at six months by combining FGG strips with XCM (4.53 mm ± 0.74) compared to FGG alone (4.73 mm ± 0.96) [29], though not statistically significant.

In the randomized controlled study by Farooqui et al. (2023), the mean width of keratinized mucosa at six months was 4.53 ± 0.74 mm in the FGG strip + XCM group, and 4.73 ± 0.96 mm in the FGG-alone group, compared with baseline values of 0.90 ± 0.28 mm and 0.87 ± 0.23 mm, respectively [29]. The corresponding changes calculated from the reported group means were +3.63 mm and +3.86 mm. The authors reported no statistically significant between-group difference in keratinized mucosa gain [29].

Studies primarily evaluated mucosal thickness in HA and i-PRF [30,32]. In the study by Bawankar et al. (2024), the six-month keratinized tissue width (KTW) was 2.44 ± 0.84 mm in the microneedling-alone group and 4.34 ± 1.02 mm in the microneedling + HA group, compared with baseline values of 2.67 ± 0.92 mm and 3.17 ± 1.01 mm, respectively [30]. The corresponding changes calculated from group means were −0.22 mm and +1.17 mm. For mucosal thickness (MT), the six-month values were 1.03 ± 0.11 mm and 2.48 ± 0.45 mm, compared with baseline values of 0.90 ± 0.16 mm and 1.09 ± 0.26 mm, respectively. The calculated changes were +0.14 mm and +1.40 mm. These findings represent changes in group means and should be interpreted alongside the study's reported statistical analyses and the limitations of its baseline data [30]. Likewise, i-PRF increased KMW from 1.66 ± 0.25 mm at baseline to 1.98 ± 0.07 mm at six months and was accompanied by substantial improvements in PIMT at 2 mm, increasing from 0.56 ± 0.06 mm to 1.31 ± 0.26 mm, while at 4 mm, from 0.72 ± 0.07 mm to 1.48 ± 0.32 mm. However, the absence of a control group limits causal interpretation [32].

Studies evaluating peri-implant papillary architecture have shown mixed findings. Bertl et al. (2017) reported no significant improvements in papillary height, black triangle dimensions, or mucosal volume following HA injections compared with saline [28]. In contrast, Bawankar et al. (2024) observed significant improvements in papillary recession height and papillary fill when injectable HA was combined with microneedling [30] (Table *4*).

Study	Intervention (test)	Comparator	Mean age (years)	Outcome	Reported results	Between group statistical results
Bertl et al., 2017 [28]	Hyaluronic acid (HA) injections	Saline injections	Test: 26.7 ± 5.2; control: 33.1 ± 6.0	Pain during first injection (VAS)	HA: 57.1 ± 23.6; saline: 49.2 ± 16.3	Not significant (P = 0.388)
				Pain during second injection (VAS)	HA: 56.2 ± 19.4; saline: 61.9 ± 19.3	Not significant (P = 0.507)
				Pain within 1 week after first injection (VAS)	HA: 27.6 ± 28.6; saline: 5.0 ± 13.8	Significant; higher pain in HA group (P= 0.034)
				Pain within 1 week after second injection (VAS)	HA: 25.8 ± 38.3; saline: 1.7 ± 5.4	Not significant (P = 0.064)
				Papillary height, black triangle dimensions and mucosal volume	No conspicuous clinical volume augmentation; no significant differences in papilla-related outcomes	No significant benefit demonstrated
Farooqui et al., 2023 [29]	FGG strip + xenogeneic collagen matrix (XCM)	FGG alone	Test: 30.80 ± 9.63; control: 29.33 ± 8.02	KMW at baseline	Test: 0.90 ± 0.28 mm; control: 0.87 ± 0.23 mm	Not significant
				KMW at 1 month	Test: 5.07 ± 0.59 mm; control: 5.13 ± 1.19 mm	Not significant between groups
				KMW at 6 months	Test: 4.53 ± 0.74 mm; control: 4.73 ± 0.96 mm	Not significant between groups
				Pink Esthetic Score (PES) at 6 months	Test: 12.20 ± 0.41; control: 10.73 ± 0.46	Significant; favoured FGG strip + XCM (P < 0.001)
				Postoperative pain/morbidity	Lower pain and morbidity with FGG strip + XCM	Significant; favoured FGG strip + XCM
Bawankar et al., 2024 [30]	Injectable HA + microneedling	Microneedling alone	Test: 28.17 ± 2.58; control: 29.33 ± 2.23	KMW at 6 months	Test: 4.34 ± 1.02 mm; control: 2.44 ± 0.84 mm	Significant increase in both groups
				Peri-implant mucosal thickness (PIMT) at 6 months	Test: 2.48 ± 0.45 mm; control: 1.03 ± 0.11 mm	Significant increase in both groups
				Interproximal width (IPW) at 6 months	Test: 0.90 ± 0.16 mm; control: 2.19 ± 0.52 mm	Test: Significant variations; control: Did not exhibit significant changes
				Papillary recession height (PRH) at 6 months	Test: 0.88 ± 0.25 mm; control: 1.67 ± 0.32 mm	Test: Significant variations; control: Did not exhibit significant changes
Temmerman et al., 2018 [31]	Leukocyte- and platelet-rich fibrin (L-PRF)	Free gingival graft (FGG)	51.6 ± 7.1	Keratinized mucosa width (KMW) gain	L-PRF: 6.0 ± 0.8 mm; FGG: 7.3 ± 1.2 mm; additional gain with FGG: 1.3 ± 0.9 mm	Significant; greater gain with FGG (P < 0.05)
				Postoperative pain/discomfort	Lower postoperative pain with L-PRF than FGG	Significant; favoured L-PRF
Chittabathina				PIMT at 4 mm from the mucosal margin	Baseline: 0.72 ± 0.07 mm; 3 months: 0.72 ± 0.07 mm; 6 months: 1.48 ± 0.32 mm	Within-group improvement reported (statistically significant); no between-group comparison possible
					Baseline: 1.66 ± 0.25 mm;	Within-group improvement

et al., 2026 [32]	i-PRF + MN	No concurrent control group	As above	KMW	3 months: 1.92 ± 0.12 mm; 6 months: 1.98 ± 0.07 mm	reported (significant increased); no between-group comparison possible
				PES/esthetic outcome	Baseline: 10.0 ± 0.85; 3 months: 10.5 ± 0.90; 6 months: 11.2 ± 0.86	Within-group improvement reported (statistically significant); no between-group comparison possible

TABLE 4: Numerical results and outcome-specific between-group comparisons

FGG: free gingival graft; HA: hyaluronic acid; i-PRF: injectable platelet-rich fibrin; IPW: interproximal width; KMW: keratinized mucosa width; L-PRF: leukocyte- and platelet-rich fibrin; PRH: papillary recession height; PIMT: peri-implant mucosal thickness; PES: Pink Esthetic Score; VAS: visual analogue scale; XCM: xenogeneic collagen matrix

Values are reported as mean ± standard deviation unless otherwise stated. “Not significant” refers to the between-group comparison unless explicitly identified as a within-group comparison. Outcomes not assessed should be marked “NA”; outcomes assessed but with numerical data unavailable should be marked “NR.” For single-arm studies, between-group statistical comparisons are not applicable.

Patient-Reported Outcome Measures (PROMs)

PROMs were reported in all included studies, although the assessment methods varied. Minimally invasive biologic interventions generally demonstrated lower postoperative morbidity than conventional grafting procedures. L-PRF was associated with significantly lower postoperative pain and shorter surgical time than FGG [31], while FGG combined with XCM yielded improved esthetic outcomes and lower postoperative discomfort compared with FGG alone [29]. I-PRF also improved patient satisfaction, pain scores, and Pink Esthetic Score during follow-up [32,33]. Bawankar et al. (2024) described their PROM assessment as a VAS; however, they provided insufficient methodological information about the instrument, including its scale structure, anchors, and validation [30]. Bertl et al. (2017) reported similar discomfort immediately after both HA and saline injection sessions. Interestingly, discomfort from injections was statistically significant only after a week following the first HA and saline injection sessions [28]. The reported responses used categorical, frequency-based options rather than a conventional continuous VAS score. This lack of clarity may make the patient-reported outcomes harder to interpret and limits direct comparability with studies using validated VAS or other standardized PROM instruments (Table *5*).

Study	KMW	PIMT	Papilla/recession parameters	Peri-implant parameters	PROMs	Esthetic outcomes	Main efficacy findings	Morbidity findings
Bertl et al., 2017 [28]	/	Volume change	PT-CP, MPIS, black triangle area	PD, CAL, BoP, plaque	Pain VAS	Patient and examiner VAS	No significant improvement with HA compared with saline	Similar discomfort immediately after first and second injections in both groups. Statistically significant discomfort in the first weeks after the first injection.
Temmerman et al., 2018 [31]	/	X	X	X	Pain scores	X	FGG superior for KMW gain	L-PRF associated with less pain and shorter surgery time
Farooqui et al., 2023 [29]	/	X	X	X	Pain VAS	PES	KMW gain and better esthetics	Lower morbidity in FGG + XCM
Bawankar et al., 2024 [30]	/	/	PRH, IPW	PI, GI, SBI, CAL, PIPD	PROMS questionnaire	Papillary fill	HA+MN improved PIMT, KMW, and papillary fill	No significant differences in PROMs
Chittabathina et al., 2026 [32]	/	/	X	X	Pain VAS	PES, VAS (patient satisfaction)	iPRF + MN enhance PIMT and improve KMW	Significant improvement in PROM's, e.g., PES, patient satisfaction, and patient pain score

TABLE 5: Outcome measures and results

HA: hyaluronic acid; MPIS: Modified Papilla Index Score; KMW: keratinized mucosa width; PIMT: peri-implant mucosal thickness; FGG: free gingival graft; L-PRF: leukocyte and platelet rich fibrin; PRH: papillary recession height; IPW: interproximal width; MN: microneedling; i-PRF: injectable platelet rich fibrin; PROMs: patient-reported outcome measures; SBI: Sulcus Bleeding Index; GI: Gingival Index; PI: Plaque Index; XCM: xenogeneic collagen matrix; PT-CP: papilla tip and contact point; VAS: Visual Analogue Scale; PD: probing depth; PIPD: peri-implant probing depth; BoP: bleeding on probing; CAL: clinical attachment level; PES: Pink Esthetic Score; /: assessment is done; X: no assessment is done

Risk of Bias of Included Studies

Of five included studies, four were designed as RCTs [28-31]. Overall risk of bias was assessed as some concern. The risk of bias assessed for five key domains was of some concern in one to three key domains in all four trials (Figure *2*).

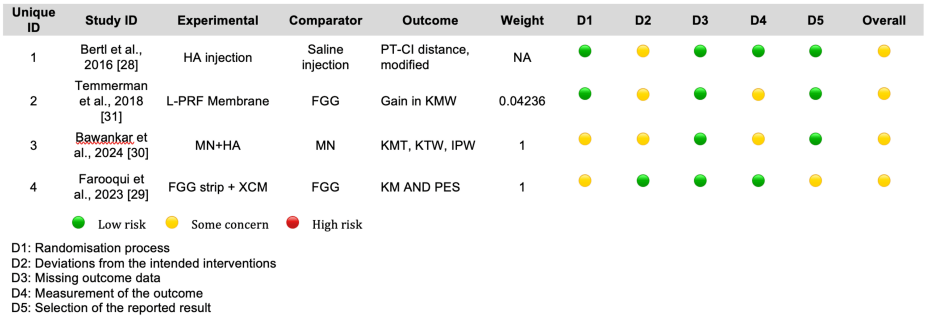


FIGURE 2: Risk of bias (RoB) assessment of RCT studies using RoB 2 tool

HA: hyaluronic acid; KMW: keratinized mucosa width; KMT: keratinized mucosal thickness; KM: keratinized mucosa; KTW: keratinized tissue width; FGG: free gingival graft; L-PRF: leukocyte and platelet rich fibrin; IPW: interproximal width; MN: microneedling; XCM: xenogeneic collagen matrix; PT-CP: papilla tip and contact point; PES: Pink Esthetic Score; RCT: randomized controlled trial

Chittabathina et al. (2026) was appraised using the NIH Quality Assessment Tool for Before-After (Pre-Post)

Studies With No Control Group because it was a prospective single-arm study without a concurrent comparator [25,32]. The study reported improvements in PIMT and KMW after i-PRF combined with microneedling; however, the small sample size and lack of a control group limit causal inference. The overall appraisal was provisionally rated as poor. The main limitation is the uncontrolled single-arm design, which means observed pre-post changes cannot confidently be attributed to i-PRF plus microneedling rather than natural variation, concurrent care, measurement effects, or other explanations. The small sample and unresolved details about eligibility, blinding, and missing data further reduce confidence (Table 6).

No.	NIH criterion	Chittabathina et al., 2026 [32]
1	Was the study question or objective clearly stated?	Yes
2	Were eligibility/selection criteria prespecified and clearly described?	Yes
3	Were participants representative of the eligible clinical population?	No
4	Were all eligible participants meeting entry criteria enrolled?	Not reported
5	Was the sample size sufficiently large to provide confidence in the findings?	No
6	Was the intervention clearly described and delivered consistently?	Yes
7	Were outcome measures prespecified, clearly defined, valid/reliable, and assessed consistently?	No
8	Were outcome assessors blinded to the intervention?	Not reported
9	Was loss to follow-up ≤20%, and were those lost accounted for in analysis?	Yes
10	Did statistical methods examine pre–post changes and provide p-values?	Yes
11	Were outcomes measured multiple times before and after intervention (interrupted time-series design)?	No
12	For a group-level intervention, did analysis account for individual-level data?	Not applicable

TABLE 6: Quality assessment tool for non-randomized study without control group

NIH: National Institutes of Health

Certainty of Evidence for Clinical Outcomes

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for each critical and important outcome [27]. The overall certainty ranged from low to high across the evaluated outcomes (Table 7). The main reasons for downgrading were methodological limitations, imprecision arising from small sample sizes, and clinical heterogeneity in the interventions, comparator groups, outcome definitions, and measurement methods.

Clinical outcome	No of studies	Participants	Effect/direction of effect	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
KMW	Temmerman et al., 2018 [31]	8	FGG produced greater gain than L-PRF	Serious	Serious	Not serious	Serious	Undetected	Very low ⊕○○○
	Farooqui et al., 2023 [26] [29]	30	FGG + XCM comparable to FGG	Not serious	Not serious	Not serious	Not serious	Undetected	High ⊕⊕⊕⊕
	Bawankar et al., 2024 [30]	65	HA + MN increased KMW compared with MN alone	Not serious	Serious	Not serious	Not serious	Undetected	Moderate ⊕⊕⊕○
PIMT	Bawankar et al., 2024 [30]	65	HA + MN significantly increased MT	Not serious	Serious	Not serious	Not serious	Undetected	Moderate ⊕⊕⊕○
	Chittabathina et al., 2026 [32]	15	i-PRF + MN showed progressive improvement	Serious	Serious	Serious	Serious	Undetected	Very low ⊕○○○
Papillary/recession parameters	Bawankar et al., 2024 [30]	65	HA + MN improved papillary fill	Not serious	Serious	Not serious	Not serious	Undetected	Moderate ⊕⊕⊕○
	Bertl et al., 2016 [28]	22	HA showed no significant improvement compared with saline	Not serious	Not serious	Not serious	Serious	Undetected	Moderate ⊕⊕⊕○
Peri-implant clinical parameters	Bawankar et al., 2024 [30]	65	No consistent evidence of clinically important changes in PD, CAL, BoP or plaque-related parameters	Not serious	Serious	Not serious	Not serious	Undetected	Moderate ⊕⊕⊕○
	Bertl et al., 2016 [28]	22	No consistent evidence of clinically important changes in PD, CAL, BoP or plaque-related parameters	Not serious	Serious	Serious	Serious	Undetected	Very low ⊕○○○
Postoperative pain/morbidity	Temmerman et al., 2018 [31]	8	L-PRF associated with less pain than FGG	Serious	Not serious	Not serious	Serious	Undetected	Low ⊕⊕○○
	Farooqui et al., 2023 [29]	30	FGG + XCM associated with lower morbidity than FGG	Not serious	Not serious	Not serious	Not serious	Undetected	High ⊕⊕⊕⊕
	Bawankar et al., 2024 [30]	65	HA + MN showed no clear PROM advantage	Not serious	Not serious	Not serious	Not serious	Undetected	High ⊕⊕⊕⊕
	Bertl et al., 2016 [28]	22	Discomfort lasted longer in HA group after injection	Not serious	Not serious	Not serious	Serious	Undetected	Moderate ⊕⊕⊕○
	Chittabathina et al., 2026 [32]	15	PROMs showed significant improvement	Serious	Serious	Serious	Serious	Undetected	Very low ⊕○○○
Esthetic outcomes/PES	Farooqui et al., 2023 [29]	30	FGG + XCM showed favourable esthetic outcomes	Not serious	Not serious	Not serious	Not serious	Undetected	High ⊕⊕⊕⊕
	Chittabathina et al., 2026 [32]	15	i-PRF showed favourable esthetic outcomes	Serious	Serious	Serious	Serious	Undetected	Very low ⊕○○○

TABLE 7: GRADE certainty of evidence for clinical outcomes

HA: Hyaluronic Acid; KMW: Keratinized Mucosa Width; PIMT: Peri-Implant Mucosal Thickness; MT: Mucosal Thickness; FGG: Free Gingival Graft; L-PRF: Leukocyte and Platelet Rich Fibrin; i-PRF: Injectable Platelet Rich Fibrin; MN: Microneedling; XCM: Xenogeneic Collagen Matrix; PES: Pink Esthetic Score; PD: Probing Depth; CAL: Clinical Attachment Level; BoP: Bleeding On Probing; PROMs: Patient-Reported Outcome Measures; GRADE: Grading of Recommendations Assessment, Development and Evaluation

Keratinized mucosal width (KMW): The certainty of evidence for KMW was rated as low. Available studies suggested that free gingival grafting (FGG) provided a more predictable increase in KMW than leukocyte- and platelet-rich fibrin (L-PRF) [31], while combining hyaluronic acid (HA) with microneedling was associated with a greater increase in KMW than microneedling alone [30]. However, these findings came

from a limited number of studies with relatively small samples and different intervention protocols. We downgraded the certainty because of concerns about risk of bias and imprecision. Differences in the interventions and comparators also limited the consistency and comparability of the findings. Consequently, the available evidence suggests potential differences in KMW outcomes, but confidence in the magnitude of these effects remains limited.

Peri-implant mucosal thickness (PIMT): The certainty of evidence for PIMT was rated as very low. Available findings suggested that HA treatment [30] and injectable platelet-rich fibrin (i-PRF) [32] might increase peri-implant mucosal thickness. Nevertheless, limited study populations, variation in treatment protocols, and the inclusion of uncontrolled clinical observations limited the evidence. The non-randomized evidence was particularly susceptible to confounding and selection bias. In addition, limited precision and short follow-up periods reduced confidence in the findings. Therefore, interpret the apparent improvements in mucosal thickness cautiously, as the true effects of these interventions remain uncertain.

Papillary fill and recession-related outcomes: The certainty of evidence for papillary and recession-related outcomes was rated as very low. Some studies reported favorable changes following biologically active treatments, including HA-based interventions [28,30]. However, the limited number of participants, variation in clinical assessment methods, and differences in intervention protocols restricted the reliability and comparability of the results. Concerns regarding risk of bias and imprecision further reduced confidence in the estimated effects. The current evidence is therefore insufficient to establish whether these interventions produce consistent and clinically meaningful improvements in papillary fill or recession-related parameters.

Peri-implant clinical parameters: The certainty of evidence for clinical parameters was rated as very low. Although some studies reported favourable changes in peri-implant clinical measurements following soft tissue augmentation, methodological weaknesses, small sample sizes, and heterogeneity in the outcomes assessed limited the findings. The short follow-up periods also restricted the assessment of longer-term clinical stability [28,30]. Accordingly, the available evidence does not support firm conclusions about the comparative effectiveness of biologically active agents and biomaterials for peri-implant clinical health.

Postoperative pain and morbidity: The certainty of evidence for patient-reported pain and postoperative morbidity was rated as low. Available studies suggested that L-PRF-based procedures may be associated with less postoperative pain and shorter surgical time than FGG [31], while combining FGG with a xenogeneic collagen matrix (XCM) might reduce postoperative morbidity [29]. However, few studies reported these outcomes, and differences in outcome assessment and intervention protocols limited comparability. Concerns regarding risk of bias and imprecision reduced confidence in the estimated effects. These findings suggest potential patient-centred benefits, although further well-designed studies are required to establish their magnitude and consistency.

Esthetic outcomes and patient satisfaction: The certainty of evidence for esthetic outcomes and patient satisfaction was rated as very low. Some studies reported improvements in Pink Esthetic Score (PES), patient satisfaction, and postoperative comfort following injectable PRF or combined grafting procedures [29,32]. For example, one study reported higher PES values following FGG combined with XCM than following FGG alone [29]. However, the evidence was based on a small number of participants and studies, with variation in treatment protocols and assessment methods. These limitations, together with concerns regarding risk of bias and imprecision, reduced confidence in the findings. Furthermore, the inconsistent reporting of patient-reported outcome measures limited the ability to draw robust conclusions about the esthetic benefits of the interventions.

Overall, the GRADE assessment indicated that the available evidence supporting biologically active agents and biomaterials for peri-implant soft tissue augmentation remains limited. Although selected clinical and patient-reported outcomes showed favourable findings, the low-to-very-low certainty ratings indicate that further research may substantially alter the estimated effects and confidence in these findings. The results should therefore be interpreted as preliminary rather than definitive evidence of comparative effectiveness.

Discussion

Peri-implant soft tissue phenotype influences peri-implant tissue stability, esthetic outcomes, and long-term maintenance of peri-implant health. Accordingly, peri-implant soft tissue augmentation procedures have been advocated to increase KMW, improve PIMT, and optimize esthetic outcomes, particularly in patients presenting with thin peri-implant phenotype or deficient keratinized mucosa [34-36].

This systematic review evaluated the clinical effectiveness of biologically active agents and biomaterials for managing PSTD. Although only five clinical studies fulfilled the eligibility criteria, the overall findings indicate that biologically active therapies may provide clinically meaningful improvements in peri-implant soft tissue dimensions while reducing surgical morbidity in selected clinical situations. i-PRF and HA, particularly when combined with microneedling, consistently improved peri-implant mucosal thickness and keratinized mucosal width [30,32].

A key finding of this review was that FGG remained the most predictable approach for increasing KMW. Although all soft tissue augmentation procedures improved at least one clinical outcome, autogenous grafting consistently achieved the greatest increase in keratinized tissue. Temmerman et al. (2018) reported significantly greater KMW gain with FGG than with L-PRF, while Farooqui et al. (2023) showed that combining FGG with a xenogeneic collagen matrix (XCM) produced KMW gains comparable to conventional FGG, with the added benefits of improved esthetics and reduced postoperative morbidity [29,31]. Collectively, these findings indicate that although biologically active materials and soft tissue substitutes may enhance wound healing and improve patient comfort, autogenous grafts remain the most predictable option when substantial augmentation of keratinized mucosa is the primary treatment objective.

Despite these promising findings, interpret the available evidence with caution. The included studies exhibited considerable heterogeneity in patient populations, defect characteristics, intervention protocols, biologic agent preparation methods, outcome measures, and follow-up durations. This methodological diversity precluded quantitative synthesis and limited meaningful comparison of treatment effects across studies. In addition, most studies reported only short- to medium-term outcomes, restricting the assessment of the long-term stability of peri-implant soft tissue improvements. These limitations align with those reported in the broader literature, where variability in study design, outcome reporting, and methodological approaches continues to impede direct comparisons and limit the formulation of robust, evidence-based clinical recommendations.

The superiority of FGG observed in this review is consistent with previous systematic reviews and current consensus recommendations on peri-implant soft tissue augmentation. Autogenous soft tissue grafts were shown to provide greater increases in keratinized mucosal width and peri-implant soft tissue volume than currently available soft tissue substitutes, particularly with respect to long-term dimensional stability [37]. Similarly, a 2021 review reported that autogenous grafting remains the most predictable approach for increasing peri-implant keratinized tissue, despite continued advances in collagen-based substitutes and biologically active materials [38]. These findings are further supported by recent consensus statements from the International Team for Implantology (ITI) and the European Federation of Periodontology (EFP), which recommend autogenous soft tissue grafts when clinically significant soft tissue augmentation is required because of their superior clinical predictability and long-term stability [39,40]. However, the extent of these clinical benefits appears to depend on factors such as the clinical indication, surgical technique, and augmentation material employed. Current evidence further supports autogenous soft tissue grafts as the most predictable approach for increasing keratinized mucosal width and peri-implant soft tissue volume, whereas soft tissue substitutes primarily offer reduced donor-site morbidity and improved patient comfort [41-43].

The clinical predictability of FGG may stem from transplantation of mature keratinized epithelium and underlying connective tissue, providing immediate tissue augmentation and facilitating stable integration at the recipient site [44,45]. In contrast, biologically active agents primarily modulate endogenous healing responses and therefore depend on the regenerative potential of the recipient tissues [46,47]. Autogenous grafts provide a structural tissue component that can maintain volume and tissue characteristics during wound maturation, which may account for their greater effectiveness in sites with pronounced keratinized tissue deficiency or unfavorable soft tissue phenotypes. This biological basis may explain the consistently greater gains in KMW observed with FGG compared with L-PRF, despite the latter's potential to promote tissue healing and regeneration [31,48,49].

Nevertheless, the present review also identified important limitations of autogenous grafting. Donor-site morbidity, longer surgical time, postoperative discomfort, and limited tissue availability may adversely affect patient acceptance. In the included studies, L-PRF and FGG combined with XCM were associated with lower postoperative pain, shorter procedures, and more favourable esthetic outcomes than conventional FGG [29,31]. These findings align with previous evidence that PROMs are increasingly relevant to treatment selection, particularly in elective implant therapy, where several approaches may provide clinically acceptable outcomes [42,50].

Collagen matrices have emerged as potential alternatives or adjuncts to autogenous grafting, primarily by providing a three-dimensional scaffold that supports cellular migration, angiogenesis, and extracellular matrix formation while avoiding donor-site morbidity [51,52]. In the present review, adding XCM to FGG maintained the clinical effectiveness of conventional grafting while improving patient-reported comfort and esthetic outcomes [29]. These findings support using collagen matrices as adjunctive biomaterials, particularly when reducing surgical morbidity is a key treatment consideration. However, the available evidence remains insufficient to support their consistent use as substitutes for autogenous grafts. Previous systematic reviews have similarly reported favourable soft tissue outcomes with collagen matrices, although the magnitude and long-term stability of tissue augmentation generally remain less predictable than those achieved with autogenous grafts [43,51].

Clinically, treatment selection should consider outcomes beyond the magnitude of tissue augmentation. FGG remains the preferred approach when substantial keratinized mucosal augmentation is required, whereas biomaterial-assisted procedures may suit patients prioritising reduced postoperative morbidity, shorter surgical time, or avoidance of a donor site. Treatment should therefore be individualized according

to defect characteristics, peri-implant phenotype, patient preferences, and overall treatment objectives, rather than applying a single approach across all clinical situations [42,53,54].

A notable finding of this review was the potential of biologically active therapies, particularly i-PRF and HA, to improve peri-implant soft-tissue dimensions. Although evidence was limited, both interventions were associated with increases in PIMT [30,32]. HA combined with microneedling also resulted in greater gains in KMW and papillary fill than microneedling alone [30], while repeated i-PRF injections produced progressive improvements in mucosal thickness and keratinized tissue dimensions over six months [32]. These findings suggest that biologically active agents may help modify thin peri-implant soft tissue phenotypes, particularly when the primary treatment objective is to improve tissue characteristics rather than replace substantial tissue deficiency.

The clinical improvements observed with i-PRF are biologically plausible given its regenerative properties. As a second-generation autologous platelet concentrate, i-PRF contains a fibrin matrix enriched with platelets, leukocytes, and bioactive mediators, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF). These mediators may promote angiogenesis, fibroblast proliferation, collagen synthesis, and extracellular matrix remodelling, thereby supporting soft tissue healing. Unlike conventional platelet-rich plasma, i-PRF is prepared without anticoagulants, allowing gradual growth-factor release during healing. Experimental and clinical evidence suggests that i-PRF can enhance fibroblast activity, collagen deposition, and vascularization, potentially explaining the progressive increases in peri-implant mucosal thickness observed in the present review [55-57]. However, mechanistic plausibility should not be interpreted as evidence of clinical effectiveness, particularly given that only one uncontrolled clinical study evaluated i-PRF [32].

HA also demonstrated potential clinical benefits, particularly when combined with microneedling. As a naturally occurring glycosaminoglycan, HA contributes to extracellular matrix organization, tissue hydration, cellular migration, and regulation of inflammatory responses [58-61]. Its effects on fibroblast activity, angiogenesis, and wound healing provide a biological rationale for its use as an adjunct in peri-implant soft tissue management [60,62]. In this review, HA combined with microneedling produced greater improvements in PIMT, KMW, and papillary fill than microneedling alone [30]. These findings suggest that HA may enhance the local healing response and support soft tissue phenotype modification, although the limited evidence warrants cautious interpretation.

Nevertheless, HA findings should be interpreted cautiously because the available evidence is limited and inconsistent. Bertl et al. (2016) reported no significant improvements in papillary height, black triangle dimensions, or mucosal volume after repeated HA injections compared with saline, whereas Bawankar et al. (2024) reported significant improvements when HA was combined with microneedling [28,30]. This discrepancy may reflect differences in study populations, treatment objectives, and application protocols. Bertl et al. (2016) evaluated HA as a stand-alone injectable treatment for deficient interproximal papillae, whereas Bawankar et al. (2024) assessed HA as an adjunct to microneedling in patients with thin peri-implant soft tissue phenotypes [28,30]. These interventions address different clinical objectives. Papillary reconstruction depends on factors beyond soft-tissue volume, including interproximal bone height, implant position, prosthetic contour, and the distance between the contact point and the bone crest. Therefore, increasing soft-tissue volume alone may be insufficient when underlying anatomical conditions are unfavourable. In contrast, increasing mucosal thickness in a thin phenotype may be a more achievable treatment objective, potentially explaining the more favourable outcomes observed with HA combined with microneedling [30].

Adjunctive microneedling may have contributed to the clinical improvements observed with HA [30]. Controlled micro-injury induces a local wound-healing response involving platelet activation, growth factor release, angiogenesis, and collagen remodelling, which may support soft tissue repair [63]. Microneedling may also facilitate the local delivery and tissue penetration of HA, potentially enhancing its biological effects. However, evidence for microneedling in peri-implant soft tissue management remains limited. Because only one study [30] in this review evaluated the combination of HA and microneedling, the current findings should be considered preliminary. Further well-designed RCTs are needed to establish clinical effectiveness, an optimal treatment protocol, and long-term stability before routine clinical use can be recommended.

Despite the encouraging findings with biologically active therapies, improvements in soft tissue dimensions should not be interpreted as evidence of long-term clinical stability. None of the included studies had a follow-up period exceeding six months, leaving the durability of increases in mucosal thickness and keratinized tissue uncertain. Peri-implant soft tissues may continue to remodel after augmentation, and tissue contraction, collagen remodelling, and functional loading may affect early dimensional gains. Accordingly, the current evidence supports short-term clinical benefits but does not establish sustained treatment stability. Long-term prospective studies using standardized outcome measures and extended follow-up are needed to determine the durability of biologically active therapies in peri-implant soft tissue management.

Collectively, the findings suggest that biologically active therapies primarily enhance peri-implant soft tissue quality by modulating endogenous healing rather than replacing deficient tissue. This distinction matters clinically: autogenous grafts remain the preferred approach when substantial soft tissue augmentation is needed, whereas i-PRF and HA may be more useful for modifying the soft tissue phenotype, supporting healing, and reducing surgical morbidity. Therefore, consider using them as complements to established grafting procedures rather than direct substitutes, pending higher-quality evidence demonstrating comparable long-term clinical stability.

Beyond conventional clinical parameters, PROMs and esthetic outcomes are increasingly recognized as important components of treatment success in implant dentistry. Current treatment objectives extend beyond peri-implant tissue stability to include reduced surgical morbidity, patient comfort, and satisfactory esthetic integration [64]. In the present review, biologically based interventions generally demonstrated favourable patient-centred outcomes compared with conventional surgical approaches. L-PRF was associated with lower postoperative pain and shorter surgical time than FGG [31], while FGG combined with XCM provided comparable clinical effectiveness with improved esthetic outcomes and reduced postoperative discomfort [29]. Repeated i-PRF injections were also associated with improvements in patient satisfaction, pain scores, and Pink Esthetic Scores (PES) during follow-up [32].

These findings are consistent with evidence supporting minimally invasive approaches as a means of reducing treatment-related morbidity and improving postoperative recovery. Injectable biologic therapies and collagen-based substitutes avoid the secondary donor site required for autogenous graft harvesting, potentially reducing surgical trauma and postoperative discomfort. These considerations may be particularly relevant in esthetic implant therapy, where patient expectations for both the treatment experience and esthetic outcomes are high. However, differences in PROM instruments, follow-up periods, and esthetic assessment methods across studies limit direct comparison and warrant standardized patient-centred outcome reporting in future trials.

Nevertheless, improvements in objective clinical parameters were not consistently accompanied by superior PROMs. Although Bawankar et al. (2024) reported significant increases in mucosal thickness and KMW following HA combined with microneedling, they observed no significant differences in PROMs compared with microneedling alone [30]. This discrepancy suggests that clinically detectable changes may not translate into meaningful benefits from the patient's perspective. Patient expectations, baseline symptoms, individual perceptions, and the magnitude of clinical change may all influence satisfaction independently of objective treatment outcomes.

The included studies used different instruments to assess postoperative pain, esthetic satisfaction, and overall treatment experience, limiting direct comparison across interventions. Future trials should incorporate validated, standardized PROMs relevant to peri-implant soft tissue augmentation to better assess patient-perceived treatment benefits and enable meaningful comparisons across studies.

Strengths and limitations

The present systematic review has several strengths. We conducted a comprehensive search strategy across multiple electronic databases, supplemented by hand searching to maximise study identification. We selected studies using a structured screening process in accordance with the PRISMA guidelines and assessed methodological quality using validated risk-of-bias tools. This review also evaluated biologically active agents and biomaterials for peri-implant soft tissue augmentation, an emerging area with limited high-quality clinical evidence.

Despite these strengths, several limitations should be considered when interpreting this review's findings. First, only five studies met the eligibility criteria, reflecting the limited availability of high-quality clinical evidence on biologically active agents and biomaterials for peri-implant soft tissue augmentation. Although four included studies were RCTs, one was a non-randomized clinical study without a control group, reducing the overall certainty of the evidence. In addition, the relatively small sample sizes and short follow-up periods, none exceeding six months, prevented evaluation of the long-term stability and sustainability of the reported clinical outcomes.

Methodological heterogeneity among the included studies further limited the interpretation of the findings. Differences in patient characteristics, peri-implant defect morphology, intervention protocols, preparation methods for biologically active agents, application frequency, comparator groups, outcome definitions, and measurement techniques prevented meaningful quantitative synthesis and restricted this review to a qualitative analysis. Furthermore, the inconsistent assessment and reporting of patient-reported outcome measures and esthetic parameters reduced comparability across studies and limited the identification of clinically meaningful treatment effects.

Another important limitation was the lack of standardized protocols for biologically active therapies. Variations in platelet concentrate preparation, HA formulations, and treatment protocols likely influence biological activity and clinical performance, contributing to the variability observed across studies.

Consequently, although the available evidence suggests these therapies may improve peri-implant soft tissue outcomes, interpret the findings with caution until larger, well-designed RCTs with standardized methodologies and longer follow-up periods become available.

Clinical implications

This review's findings have important clinical implications for managing PSTD. Treatment selection should be individualized according to defect characteristics, peri-implant phenotype, esthetic requirements, and patient preferences. FGG remains the most predictable approach for increasing KMW, particularly in sites with severe soft tissue deficiency, although its benefits should be balanced against donor-site morbidity and increased surgical complexity.

Biologically active agents and biomaterials may serve as useful adjuncts in selected clinical situations. i-PRF and HA demonstrated favorable effects on PIMT and soft tissue phenotype modification, suggesting potential benefits in patients with thin peri-implant tissues or when minimally invasive treatment is preferred. Similarly, XCM may reduce postoperative morbidity while providing satisfactory clinical and esthetic outcomes.

However, the current evidence does not support replacing autogenous grafts with biologically active therapies. Until robust long-term evidence is available, consider these interventions complementary to established grafting procedures rather than substitutes. Treatment decisions should therefore be guided by the clinical indication, expected treatment outcomes, and patient-centred considerations.

Conclusions

Within the limitations of the available evidence, biologically active agents and biomaterials appear to be promising adjuncts for peri-implant soft tissue augmentation. While FGG remains the gold standard for managing peri-implant soft tissue defects, other biologically active agents and biomaterials, such as i-PRF and HA, have shown favourable effects on PIMT and soft tissue phenotype modification. XCM, used with FGG, may influence post-operative morbidity and patient-centred outcomes while maintaining satisfactory clinical performance, but further comparative studies are needed. However, the limited number of studies, methodological heterogeneity, and short follow-up periods reduce the certainty of the current available evidence. Consequently, these therapies should currently be considered adjuncts rather than alternatives to autogenous soft tissue grafting.

Future research should prioritize adequately powered, multicentre RCTs with standardized intervention protocols, outcome measures, and longer follow-up to establish the long-term effectiveness of biologically active therapies. Comparative studies evaluating different biomaterials and growth factors are also needed to define their optimal clinical indications and support evidence-based treatment recommendations.

Appendices

Appendix 1: database-specific Boolean search strategies

A. Web of Science

("dental implant*" OR "peri-implant*" OR "periimplant*" OR "implant supported" OR "implant site*")

AND

("soft tissue defect*" OR "soft tissue augmentation" OR "soft tissue graft*" OR "peri-implant mucosa*" OR "keratinized mucosa" OR "keratinized gingiva" OR "keratinized tissue" OR "mucosal thickness" OR "gingival thickness" OR "soft tissue phenotype" OR "tissue augmentation" OR "mucosal recession" OR papilla*)

AND

("biologically active agent*" OR "bioactive agent*" OR biomaterial* OR "platelet-rich fibrin" OR "injectable platelet-rich fibrin" OR "leukocyte- and platelet-rich fibrin" OR "platelet concentrate*" OR "autologous platelet concentrate*" OR "hyaluronic acid" OR "collagen matrix" OR "xenogeneic collagen matrix" OR "collagen scaffold*" OR "acellular dermal matrix" OR "growth factor*" OR "fibrin matrix")

B. The Cochrane Library

dental implant* OR peri-implant* OR periimplant* OR implant-supported OR implant site* OR soft tissue defect* OR soft tissue augmentation OR soft tissue graft* OR peri-implant mucosa* OR keratinized mucosa OR keratinized gingiva OR keratinized tissue OR mucosal thickness OR gingival thickness OR soft tissue phenotype OR tissue augmentation OR mucosal recession OR papilla* OR biologically active agent* OR bioactive agent* OR biomaterial* OR platelet-rich fibrin OR injectable platelet-rich fibrin OR leukocyte- and

platelet-rich fibrin OR platelet concentrate* OR autologous platelet concentrate* OR hyaluronic acid OR collagen matrix OR xenogeneic collagen matrix OR collagen scaffold* OR acellular dermal matrix OR growth factor* OR fibrin matrix)

C. MEDLINE (PubMed)

("Dental Implants" OR "dental implant*"[tiab] OR "peri-implant*"[tiab] OR "periimplant*"[tiab] OR "implant-supported"[tiab] OR "implant site*"[tiab])

AND

("Mouth Mucosa"[Mesh] OR "Gingiva"[Mesh] OR "soft tissue defect*"[tiab] OR "soft tissue augmentation"[tiab] OR "soft tissue graft*"[tiab] OR "peri-implant mucosa*"[tiab] OR "keratinized mucosa"[tiab] OR "keratinized gingiva"[tiab] OR "keratinized tissue"[tiab] OR "mucosal thickness"[tiab] OR "gingival thickness"[tiab] OR "soft tissue phenotype"[tiab] OR "tissue augmentation"[tiab] OR "mucosal recession"[tiab] OR papilla*[tiab])

AND

("Platelet-Rich Fibrin"[Mesh] OR "Hyaluronic Acid"[Mesh] OR "Collagen"[Mesh] OR "Biocompatible Materials"[Mesh] OR "biologically active agent*"[tiab] OR "bioactive agent*"[tiab] OR biomaterial*[tiab] OR "platelet-rich fibrin"[tiab] OR "injectable platelet-rich fibrin"[tiab] OR "leukocyte- and platelet-rich fibrin"[tiab] OR "platelet concentrate*"[tiab] OR "autologous platelet concentrate*"[tiab] OR "hyaluronic acid"[tiab] OR "collagen matrix"[tiab] OR "xenogeneic collagen matrix"[tiab] OR "collagen scaffold*"[tiab] OR "acellular dermal matrix"[tiab] OR "growth factor*"[tiab] OR "fibrin matrix"[tiab])

D. Scopus

("dental implant*" OR "peri-implant*" OR "periimplant*" OR "implant-supported" OR "implant site*")

AND

("soft tissue defect*" OR "soft tissue augmentation" OR "soft tissue graft*" OR "peri-implant mucosa*" OR "keratinized mucosa" OR "keratinized gingiva" OR "keratinized tissue" OR "mucosal thickness" OR "gingival thickness" OR "soft tissue phenotype" OR "tissue augmentation" OR "mucosal recession" OR papilla*)

AND

("biologically active agent*" OR "bioactive agent*" OR biomaterial* OR "platelet-rich fibrin" OR "injectable platelet-rich fibrin" OR "leukocyte- and platelet-rich fibrin" OR "platelet concentrate*" OR "autologous platelet concentrate*" OR "hyaluronic acid" OR "collagen matrix" OR "xenogeneic collagen matrix" OR "collagen scaffold*" OR "acellular dermal matrix" OR "growth factor*" OR "fibrin matrix")

E. Europe PMC

("dental implant*" OR "peri-implant*" OR "periimplant*" OR "implant supported" OR "implant site*")

AND

("soft tissue defect*" OR "soft tissue augmentation" OR "soft tissue graft*" OR "peri-implant mucosa*" OR "keratinized mucosa" OR "keratinized gingiva" OR "keratinized tissue" OR "mucosal thickness" OR "gingival thickness" OR "soft tissue phenotype" OR "tissue augmentation" OR "mucosal recession" OR papilla*)

AND

("biologically active agent*" OR "bioactive agent*" OR biomaterial* OR "platelet-rich fibrin" OR "injectable platelet-rich fibrin" OR "leukocyte- and platelet-rich fibrin" OR "platelet concentrate*" OR "autologous platelet concentrate*" OR "hyaluronic acid" OR "collagen matrix" OR "xenogeneic collagen matrix" OR "collagen scaffold*" OR "acellular dermal matrix" OR "growth factor*" OR "fibrin matrix")

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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