The impact of hyaluronic acid application in the non-surgical treatment of periodontitis, peri-implant mucositis, and peri-implantitis: a narrative review

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ABSTRACT

Objective: Hyaluronic acid (HA) has obtained considerable attention in scientific research due to its role in biological processes and its therapeutic potential. It has been studied as an adjunctive to conventional periodontal treatment, accordingly; we aimed in this review to assess the impact of hyaluronic acid in the treatment of periodontitis, peri-implant mucositis and peri-implantitis. **Method:** An online search was conducted using the keywords (periodontitis, peri-implantitis and peri-implant mucositis) in combination with hyaluronic acid. **Results:** Seventy (70) articles were retrieved while 23 full articles showing the effect of HA as adjunctive therapy were assessed for suitability. Thirteen studies fully met the inclusion criteria and were included and analysed in the review. **Discussion:** Many studies suggested that applying HA in periodontal pockets can enhance periodontal tissue repair contributing to improved clinical outcomes; where the reported data showed that clinical attachment level, periodontal pocket depths and bleeding on probing scores were favouring the treatment with HA. There are insufficient studies addressing and talking about the application of HA in the treatment of peri-implant mucositis, and in the context of peri-implantitis, preliminary findings suggest that HA may have potential therapeutic benefits in the adjunctive management of peri-implantitis around compromised dental implants. **Conclusions:** Hyaluronic acid may have a positive and an additional effect in comparison to debridement alone on the treatment of periodontitis and promising but modest results are seen when used as an adjunct to non-surgical therapy for treating peri-implantitis and peri-implant mucositis.

Keywords: hyaluronic acid; peri-implant mucositis; peri-implantitis; periodontal pocket; periodontitis; treatment outcome

CDHA Research Agenda category: risk assessment and management

INTRODUCTION

Hyaluronic acid (HA) also known as hyaluronan is a naturally occurring non-protein glycosaminoglycan, produced by synoviocytes, fibroblasts, and chondrocytes and is normally present in joints, skin, eyes and other organs and tissues (connective, epithelial, and neural) of the body (1).

Hyaluronan synthase (HAS) is responsible for the synthesis of HA, of which three isozymes are found in vertebrates (HAS-1, HAS-2, and HAS-3). These three isozymes produce different size HA polymers, significantly; the body of a healthy adult weighing 70 kg contains approximately 15 g of HA and the highest concentration is found in typical connective tissues (1). Hyaluronic acid turnover is attributed to either local metabolism or lymphatic outflow into the circulatory system. Regardless the route of elimination, the tissue HA half-life ranges from half a day to 2 or 3 days based on its location (2); in the circulation is 2± 5 minutes and in an apparently inert tissue such as cartilage, the half-life is 1 ± 2weeks (3).

Hyaluronic acid is highly biocompatible, highly viscoelastic, and capable of retaining moisture (4). Beyond its physical properties, HA plays a crucial role in cell signaling, proliferation, migration, and morphogenesis (5, 6). And it participates in essential functions such as wound healing, regeneration and inflammation (3).

Hyaluronan plays a major part in water homeostasis and acts as a lubricant which conform to its viscosity and elasticity. Its molecular weight and concentration are positively related to both viscosity and elasticity (2). Also, HA demonstrated dose-dependent bacteriostatic effects, as it has the ability to reduce bacterial adhesion, thus biofilm formation (7).

Hyaluronic acid has been studied as an adjunctive to conventional treatment of periodontitis, peri-implant mucositis and peri-implantitis (8-10). According to a meta-analysis, the incorporation of HA as an adjunct to non-surgical periodontal therapy led to reduction in periodontal pocket depth (PPD) (average −0.36 mm), clinical attachment level (CAL) gain (average 0.73 mm), and a greater decrease in bleeding on probing (BOP) (average −15%) compared to conventional scaling and root planing after 3 months (11).

The application of HA for treating peri-implantitis is increasingly being recognized and drawing interest. As has been shown, promising outcomes have been reported in the management of peri-implant pathologies (12).

Accordingly, we aimed in this review to assess the impact of hyaluronic acid in the treatment of periodontitis, peri-implant mucositis and peri-implantitis.

METHOD

A comprehensive online search of the literature was conducted using the Pubmed database. Key MESH words used were: Hyaluronic acid, Periodontitis, Peri-implant mucositis and Peri-implantitis. Inclusion Criteria consisted of: clinical studies or randomized clinical trials published between 2014 and July 2025; studies investigating non-surgical periodontal treatment; studies published in English; and studies reporting clinical outcomes related to non-surgical periodontal treatment, such as changes in probing depth, clinical attachment level, or inflammatory markers. Excluded were: in-vitro or in-vivo animal studies, case reports; short follow-up studies; studies focusing on surgical periodontal or peri-implant treatment and those with insufficient information regarding the topic, such as failing to mention the concentration of HA or the number of treatment applications.

RESULTS

During the screening process (Figure 1), 70 articles were identified. After elimination of duplicates and those not meeting the inclusion criteria, 23 full-text articles were assessed for eligibility. After further elimination, a total of 13 articles; all of which were randomized clinical trials with various designs (e.g., split-mouth, parallel, double-blind, or single-blind) were included for analysis in the review. (Table 1). The remaining studies were excluded for reasons as shown in the flow diagram (Figure 1).

Most of the included studies focused on periodontitis, either as part of initial therapy or in the management of infrabony defects using minimally invasive non-surgical techniques, where thin ultrasonic tips and Gracey mini-curettes were employed. In contrast, there is limited evidence on the application of HA in the management of peri-implant mucositis, whereas relatively greater attention has been directed toward peri-implantitis.

The findings of all included studies are described in the Discussion section.

DISCUSSION

Hyaluronic acid (HA) is a ubiquitous glycosaminoglycan, an integral component of the extracellular matrix (1). There has been a growing focus on developing innovative drug delivery systems utilizing HA, owing to its biocompatibility and ability to form hydrogels. This has become a rich area of research, yielding informative and promising outcomes.

These systems aim to improve the targeted delivery of therapeutics for various diseases (13). Also, in combination therapies (14), researchers explore combining HA with other biomaterials

and therapeutic agents to enhance regenerative outcomes, especially in fields like neurology, cardiology, oncology and also dentistry.

In this article, we reviewed the influence of hyaluronic acid as adjunctive therapy in the treatment of periodontitis, peri-implant mucositis, and peri-implantitis.

Hyaluronic acid and periodontitis

Periodontitis is a chronic multifactorial inflammatory disease that results in clinical attachment loss and radiographically assessed alveolar bone loss. Destruction of the connective tissue by periodontal inflammation increases the gingival fluid levels of low-molecular-weight (LHW)-HA (15). High-molecular-weight (HMW-HA) inhibits the immune response and prevents excessive inflammation, whereas LHW fragments have a role in signaling tissue injury and mobilizing immune cells (16).

Hyaluronic acid with a HMW has a strong effect on downregulating genes related to the virulence and adhesion of P. gingivalis which is largely regarded as a crucial pathogen in the etiology of periodontal diseases. The observed minimum inhibitory concentration of HA against P. gingivalis was 4 mg/mL and the most efficacious concentration was 1 mg/mL, but lower amounts were linked to greater gene suppression (17).

According to the European Federation of Periodontology clinical practice guidelines in treating patients with periodontitis stages I-III, the aim of the therapy is to control the subgingival biofilm and calculus by subgingival debridement which may include the adjunctive use of physical or chemical agents (18).

Numerous studies have evaluated the application of HA gel into periodontal pockets as an adjunct to initial phase periodontal therapy, comparing its outcomes with sites that received no gel.

In a split mouth clinical trial (n=33), 0.2% hyaluronon gel (Gengigel®) was applied in the periodontal pocket following scaling and root planing (SRP) in chronic periodontitis patients and then was reapplied 1week post treatment. Pocket sites showed significant improvements in bleeding index, PPD reduction and CAL gain with p-value of (0.001) compared to the control sites (received only SRP) at the 12 week re-evaluation period (19). Similar results were demonstrated by Olszewska-Czyz and colleagues[20], where the test group showed a significantly greater gain in CAL by 1 mm, a lower percentage of sites with BOP, and a greater reduction in PPD by 0.5 mm compared to the control group at 12 weeks. In the test group, HA gel was applied to the periodontal pockets immediately after the completion of initial periodontal therapy, with a second application administered to existing pockets six weeks later (20).

A concentration of 0.8% HA gel was used in some studies. Al-Shammari et al.[21], in a split-mouth design, showed statistically significant differences in gingival index and PPD, with the test site having a significantly lower PPD than the control site by 0.4475 mm at 12 weeks. However, there was no significant difference in CAL. In this study, the gel was applied after SRP and again at a 1-week follow-up visit (21).

Vajawat et al.[22] also used 0.8 % HA gel that was inserted into the pockets immediately after SRP and then re-inserted at the 1-week interval in smoker and non-smoker groups. There were no statistically significant differences in PPD values at any time point between the test and control sites. The test sites exhibited significant greater CAL gain with a mean gain of 1.54 mm but this was only in the smoker group. This may be attributed to the fact that, within the control sites, there was a statistically significant difference in CAL scores between smokers and non-smokers at baseline (22).

In another study, a thermosensitive gel containing active 0.8% HA combined with a preservative was used. The gel remained non-viscous at 20°C and transformed into a viscous state at 37°C upon contact with the warm gingival surfaces of the periodontal pocket. The gel was applied after SRP and reapplied after one month. Regarding BOP, CAL and PPD, the test sites demonstrated significantly greater improvements compared to the control sites at both 3 and 6 months. Specifically, the CAL gains at the test sites were 2.27 mm at 3 months and 3.27 mm at 6 months, both significantly greater than the control sites. (23)

It was revealed that the adjunctive use of 0.2 % hyaluronan following mechanical debridement resulted in a comparable reduction in neutrophil elastase levels in gingival crevicular fluid (GCF) samples at 6 weeks and no significant difference in CAL and PPD between control and test sites, this may be explained by the short follow up or no re-application of the gel (24).

In regard to infrabony defects, HA can be used in conjunction with the minimally invasive non-surgical technique (MINST). Radiographically, Iorio-Siciliano et al. [25] demonstrated significantly improved cementoenamel junction to bone defect (CEJ-BD) values at 6 months in the group receiving MINST combined with cross-linked HA (4.3 ± 2.3 mm) compared to the control group treated with MINST alone (5.6 ± 1.9 mm, $p < 0.05$). However, when comparing clinical parameters such as PD and CAL, a statistically significant advantage for the test group was observed only at the 3-month follow-up. By 6 months, no statistically significant differences were found between the two groups for either PD or CAL (25).

This is in agreement with a similar study that also evaluated the effect of HA in infrabony defects, which reported a PD reduction of 3.29 ± 0.77 mm at 3 months and 3.52 ± 0.79 mm at 6 months in the test group, compared with 2.57 ± 0.96 mm and 3.89 ± 1.76 mm in the control

group; the difference was significant at 3 months ($p < 0.05$) but not at 6 months ($p > 0.05$). Radiographic evaluation revealed a significant reduction in infrabony defect depth within both groups, while total defect depth, CEJ–Alveolar crest distance, and infrabony defect angle showed no significant differences between groups (26).

Previous literature has reported varying results on the benefit of incorporating active agents into interdental cleaning devices. One study showed that patients using HA with interdental brushes experienced significant reductions in gingival bleeding, as measured by the papillary bleeding index, compared with controls (27).

Additionally, a study investigated whether adjunctive use of HA—applied subgingivally in-office and supragingivally by the patient—could enhance outcomes in periodontitis patients under supportive care, showing that repeated HA application may reduce the need for re-instrumentation and improve pocket closure, with results influenced by plaque control (28).

Moreover, the adjunctive application of HA gel has been associated with additional benefits, suggesting a potential short-term effect of local HA used alongside professional mechanical plaque removal in improving glycemic control; thus, it is plausible that the currently observed positive impact on HbA1c could be attributed to the Hawthorne effect (29).

Despite these encouraging findings, there still remains some controversy regarding the clinical outcomes of HA use in periodontal therapy. While most studies indicate that HA contributes positively to periodontal health, particularly in reducing BOP and achieving improvements in clinical attachment levels and reductions in PPD, inconsistent results have been reported. These discrepancies may be attributed to variations in HA concentrations, differences in the number

and timing of reapplications, and study-specific factors such as the severity of periodontal disease.

Hyaluronic acid and peri-implant mucositis and peri-implantitis

In peri-implant mucositis, the main clinical characteristic is bleeding on gentle probing (24). After plaque/biofilm control is restored, it could take more than 3 weeks for the resolution of this clinical sign as the microbial biofilm is considered to be the etiological factor for peri-implant mucositis (24).

Evidence for the use of HA in managing peri-implant mucositis remains limited. Among the studies excluded from our review as it did not meet our inclusion criteria, Ahmedbeyli et al.[10] investigated a mouthwash containing HA in combination with 0.2% chlorhexidine as an adjunct to basic periodontal therapy in the treatment of peri-implant mucositis. The study showed that the use of this mouthwash resulted in a higher level of treatment success and a more noticeable reduction of facultative and periodontal pathogens compared to those who did not use the adjunctive mouthwash (10).

Given the limited data on HA in peri-implant mucositis, it is worth noting that a greater number of studies have explored its role in the treatment of peri-implantitis.

Peri-implantitis is a plaque-associated pathological condition that affects the tissues surrounding dental implants. It is characterized by inflammation of the peri-implant mucosa and a gradual loss of the supporting bone (30). For the control of peri-implantitis, mechanical debridement alone is often insufficient and thus adjunctive therapies have been proposed (31); among those adjunctive modalities is HA.

A randomised clinical trial conducted on peri-implantitis patients, compared a group that received an injectable 0.8% HMW-HA gel into the peri-implant pocket in the dental office followed by application of a 0.2% HA gel by the patient at home, 3 times per day for 45 days, with the control group receiving no topical application of any compound.[9] Although findings showed more BOP reduction in the test group, only borderline significance was reached at 90 days (P value: 0.07) and without any significant differences in PPD and CAL. This investigation also included an ELISA test for the proinflammatory cytokines (interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α)) from GCF samples. Positive results favouring the test group were reported, where significantly greater reductions in IL-1β concentrations were observed in the test group compared to the control group at 45 days (P = 0.04). However, for the TNF-α, no significant difference was found. The authors concluded that the use of HMW-HA may be an effective therapeutic option to control the progression of this disease (9).

In another clinical trial, the same approach was employed to analyze the effect of HA on the subgingival microbiome in the implant site of patients suffering from peri-implantitis, which suggested that its use led to a decrease in microbial alpha diversity and microbial variability, and demonstrated that HMW-HA is effective in the early stages of peri-implantitis by reducing early colonizing bacteria and limiting their role as "bridge species," thereby preventing the subsequent colonization of orange and red complex pathogens (32).

To better understand the long-term efficacy of HA in the management of periodontitis and peri-implant diseases, further studies with larger sample sizes, extended follow-up periods (six months, twelve months, or longer), and repeated reapplications of HA at various intervals are needed to determine whether these positive effects are sustained over time.

One of the limitations of this review is that it focuses solely on the use of hyaluronic acid in the non-surgical management of periodontal conditions, without addressing its potential applications in surgical therapies.

CONCLUSION

It is critical to explore innovative ways to inhibit infections and lessen our reliance on traditional medicine. Hyaluronic acid has been studied as an adjunct to conventional periodontal treatment with promising therapeutic outcomes. Based on this review, hyaluronic acid may have a positive and additive effect when used alongside debridement in the treatment of periodontitis. While current evidence regarding its use as an adjunct to non-surgical therapy for peri-implantitis and peri-implant mucositis is limited, initial findings, although modest, are promising. Further research is necessary to establish its effectiveness and optimal use.

ETHICAL APPROVAL

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest and no generative AI or AI-assisted technologies were used in the writing, editing, or production of this manuscript.

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Figures and Tables

Figure 1. Flow diagram of the screening process

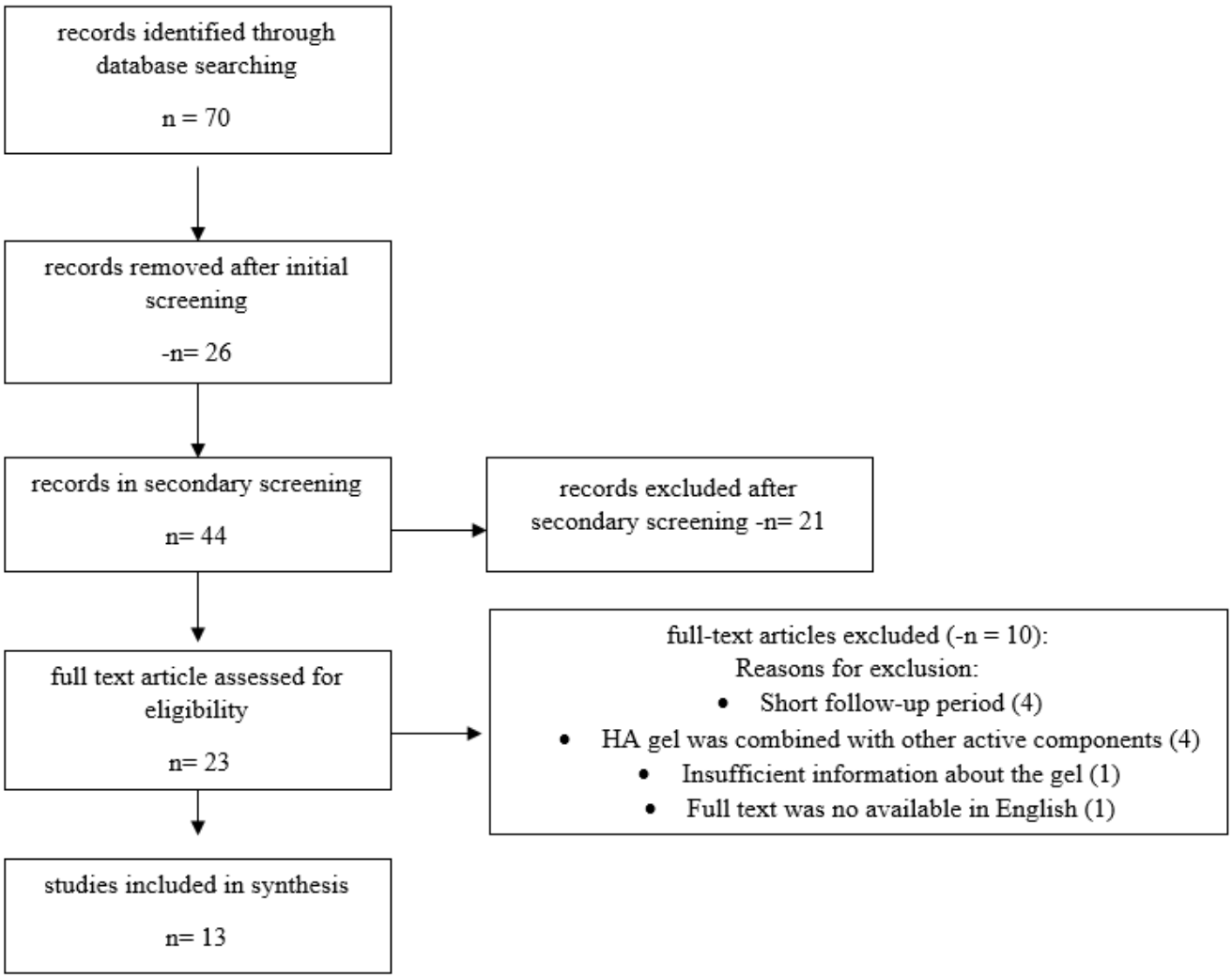

Table 1. Studies that used HA as an adjunctive therapy

Study	Participants	Treatment method used	HA dose	# of applications	Periodontal diagnosis	Results
Periodontitis						
Rajan et al. (2014)	33PTs, SMT	Control sites: SRP alone Test sites: SRP + HA	0.2 % HA	-BL after treatment - at week 1	Moderate to severe chronic periodontitis	The additional use of HA gel showed Statistically Significant development of BOP,CAL & PPD in test sites at12 weeks.
Olszewska-Czyz et al. (2021)	100 PTs, each group=50	Group 1: SRP alone Group 2: SRP + HA	The gel is a mixture of 1.6% cross-linked HA, 0.2% native HA	-BL - at week 6 at existing pockets	Localized, moderate periodontitis	More favorable clinical results in group 2 (CAL gain: 1 mm more than group 1)
Al-Shammari et al. (2018)	22 PTs, SMT	Control sites: SRP alone Test sites: SRP+HA gel	0.8 % HA	-BL - at week 1	Moderate to severe periodontitis	-Significant reduction in PPD in the Test site, and it's more pronounced at 12 weeks. -Test sites had higher levels of hBD-2 in GCF samples
Vajawat et al. (2022)	22 PTs, 44 sites. smokers and non-smokers. SMT	Control sites: SRP +placebo gel Test sites: SRP+ HA gel	0.8 % HA	-BL -at week 1	Chronic Periodontitis	-Statistically significant difference in the colony counts of Aa and Pg between the test and control sites, with a greater reduction observed in the test. -Significant difference in CAL gain at 3 months, which was maximum in the smoker group with a mean gain of 1.54 mm
Ariel et al. (2022)	34 PTs, SMT	Control sites: SRP Test sites: SRP + gel	0.8% HA combined with 0.625% octenidine	-BL - at 1 month	Stage 3 periodontitis	Statistically Significant improvement in BOP, CAL and PPD in test sites compared to

			HCl as a preservative			control sites at 6 months.
Mallikarjun et al. (2016)	20 PTs, 80 sites. SMT	Control sites: SRP Test sites: SRP + HA	0.2 % hyaluronan gel	-BL	Moderate to advanced chronic periodontitis.	-No significant difference in CAL or PPD between control and test sites at 6 weeks. -Comparable results in Neutrophil elastase in GCF samples.
Iorio-Siciliano et al. (2025)	38 patients with one intrabony defect each. Test: 19 PTs Control: 19 PTs	Control group: MINST Test Group: MINST + HA	Cross linked HA	-BL	Periodontitis (stage III or IV) periodontal pocket associated with moderate intrabony defect.	-Statistically significant difference in PPD and CAL at 3 months but not at 6 months. -At 6 months, the test group had better CEJ-BD values compared to the control group ($p < 0.05$). -Defect fill was greater in the test group.
Gundogdu Ezer U, Gunpinar S (2025)	Test group: 17, Control group : 19	Control group: MINST Test group: MINST + HA	0.8 % HA	-BL - at one month	Advanced periodontitis (stage III/IV); presence of intrabony defect with a probing depth ≥5 mm and defect depth ≥3 mm	-PD and CAL measurements showed a significant improvement in the test group compared to the control group at 3months. -Total defect depth: Decreased by 0.64 ± 0.75 mm in the control group and 1.06 ± 1.15 mm in the test group, ($p > 0.05$). - Significant Intrabony defect depth reduction in both groups at 6 months, ($p > 0.05$).
Saraç Atagün Ö, et al. (2025)	60 PTs, 180 interproximal sites (3 sites per participant)	Control group: interdental brush alone Test group:	0.2% high molecular weight sodium hyaluronate gel	Once daily after routine tooth brushing	Stage II/III, Grades A/B, generalized periodontitis	-HA gel with an interdental brush significantly improved clinical periodontal parameters,

	30 pts for each group	30 interdental brush with 0.2% HA gel				PBI/gingival bleeding was lower with HA at 1 and 3 months; -No between-group differences for PD, CAL, GI, or PI.
Bertl K, et al (2024).	56PTs, 221 experimental sites Control group: 26 PTs Test group: 30 PTs	Controls sites: SRP Placebo Test sites: SRP+HA	0.3% non-crosslinked, middle molecular weight gel	-BL - Once daily supragingivally with an interdental brush for 3 months	Generalized Stage III, Grade B periodontitis, currently under supportive periodontal care	At 12 months, a slightly higher proportion of test sites achieved pocket closure compared to control sites, although the difference was not statistically significant.
Al-Abbadi R, et al.2025	26 PTs	Control group: 13 patients; PMPR Test group : 13 patients; PMPR + HA	EZ-Cure Hyaluronic acid 0.88%	-BL - at week 1	(HbA1c < 7%) type 2 diabetic stage-II grade B periodontitis	-A statistically significant improvement of 0.13% was notable in the HbA1c values of test group over six months. -No significant intergroup differences were observed in defect depth or radiographic bone density ($p > 0.05$); however, both groups individually showed significant improvements.
peri-implantitis						
Sánchez-Fernández et al. (2021)	61 PTs, 100 implant: 21 PTs (32 implants) in the test group, 20 (32 implants) in control group 1, and 20 (36 implants) in control group 2	Test Group: HA Control group 1: xopolysaccharide (galactomannan) hydroxypropyl guar gel Control Group2 : patients received no topical application of any compound	0.8 % HMW-HA And 0.2 %	0.8 HA clinic application followed by application of the same gel (but at 0.2%) by the patient at home for 45 days	Peri-implantitis	-Among sites with a PPD ≥ 5 mm, the test group showed a significantly greater reduction in IL-1β concentrations at 45 days compared to control group 2 ($P = 0.04$). -The IL-1β concentration in the test group was 51 pg/mL lower than in control group 2

Soriano-Lerma et al. (2019)	19 patients (38 samples) in test group, 17 patients (34) in control group 1, and 18 patients (36) in control group 2	Same Above	0.8 % HA And 0.2 %	Same Above	Peri-implantitis	- 3 microbial strata were identified, each representing a distinct consortium linked to peri-implantitis - The greatest effect of HA was observed in the early colonizers (stratum 2), where 3 out of 4 early colonizers—*Streptococcus, Veillonella,* and *Rothia*—decreased after HA compared to control group 1, 2. - The lowest effect occurred in stratum 1 (environmental bacteria), where no differences were found after HA treatment.

Glossary: PT: Patients; SMT; Split Mouth Technique, SRP; scaling, root planing; BL: Baseline subgingivally after instrumentation; hBD-2: human beta defensin-2, GCF: gingival crevicular fluid; Aa: Aggregatibacter actinomycetemcomitans; Pg: Porphyromonas gingivalis; MINST: minimally invasive non-surgical technique; CEJ-BD: cementoenamel junction to bone defect; PMPR: professional mechanical plaque removal