REVIEW ARTICLE

Use of Hyaluronic Acid in Periodontal Disease Treatment: A Systematic Review

Panagiotis Karakostas[1], Sotiria Davidopoulou[2], Sotirios Kalfas[3]

Abstract

Aim: The main purpose of the present study was to investigate the potential benefit of local use of hyaluronic acid as an adjunct to periodontal therapy, since commercial products of hyaluronic acid (HA), due to its anti-inflammatory and anti-bacterial actions and its significant role in wound repair, have been proposed as adjuncts to either nonsurgical or surgical periodontal therapy.

Materials and methods: A total of 19 electronic databases were searched and the appropriate studies were identified with the use of specific eligibility criteria, according to PRISMA guidelines. Two reviewers independently screened and selected the studies and made the data extraction and the assessment of risk of bias, by using the Cochrane risk of bias tool.

Results: Out of 3,186 papers, 38 randomized clinical trials (8 related to gingivitis therapy, 20 related to nonsurgical periodontal therapy, and 10 related to surgical periodontal therapy) were finally included in the review. The outcomes were categorized as primary (that answered the focus question) and secondary (regarding additional quality characteristics). The adjunct use of HA combined to all treatment modalities shows improvement of patients' postoperative course, in terms of decreased inflammatory reactions, and changes in periodontal pocket depth and clinical attachment level. No side effects were reported in any of the included studies. Among the secondary outcomes were the variety of HA formulations and chemical forms, the variety in application, follow-up protocol and blinding design, the uneven geographic distribution of the studies, and the low bibliometric characteristics of most studies.

Conclusion: Overall and despite the positive effects reported, further research is needed to define the ideal HA compound, formulation, and regimen characteristics for periodontal disease treatment.

Clinical significance: The adjunct use of HA may lead in the reduction of the prescription of nonsteroid anti-inflammatory drugs and achieve improved clinical parameters, including periodontal probing depth, periodontal inflammation, and clinical attachment level.

Keywords: Evidence-based dentistry, Gingivitis, Inflammation, Periodontal diseases, Periodontal tissues, Treatment planning.

The Journal of Contemporary Dental Practice (2022): 10.5005/jp-journals-10024-3308

Introduction

Gingivitis and periodontitis, usually referred as periodontal diseases, are chronic biofilm-associated infections of the periodontal tissues.[1–3] The prevalence of periodontal diseases is high, globally ranging between 20 and 50%, and severe periodontitis is among the leading causes of tooth loss.[4] Management of gingivitis and periodontitis comprises conservative and surgical therapeutic strategies.[5,6] A great number of adjunct agents have been suggested to meliorate the clinical post-treatment course when combined with the chief therapeutic strategies.[7] These adjuncts comprise a number of anti-inflammatory agents, antibiotics, and antiseptics, e.g., chlorhexidine and essential oils, as well as substances that may assist healing and tissue regeneration, like enamel matrix proteins and HA.

Hyaluronic acid is a disaccharide polymer that belongs to the family of glycosaminoglycans. Native HA exists at a high-molecular-weight form (10^4–10^7 Da) in the human connective and epithelial tissues, and it comprises a major component of the extracellular matrix.[8] In the oral cavity, it constitutes a structural part of both mineralized (alveolar bone, cementum) and non-mineralized tissues (periodontal ligament, gingival tissues).[9]

Hyaluronic acid participates in many biological activities, such as phagocytosis, cell migration, and adhesion, and exerts anti-inflammatory and anti-bacterial actions demonstrating a significant role in wound repair.[10] Commercial products containing the nontoxic high-molecular-weight (1.5×10^5 Da) HA have been used as adjuncts to either nonsurgical or surgical periodontal therapy.[11] Due to its adhesive texture, the applied HA is suggested to remain in the tissues where it provides its biological actions.[11]

Until 2019, three systematic reviews dealing with the potential benefit and safety of local application of HA in periodontal apparatus were published,[12–14] but the literature search of these reviews were limited to include no more than six electronic databases and several new original research articles have recently appeared in the literature. Thus, to examine more extensively the relevant data and to include the latest trials, we decided to conduct a new systematic review by searching a larger number of electronic databases. The present systematic review aimed to investigate whether the local use of HA as an adjunct to the management

[1,3]Department of Preventive Dentistry, Periodontology and Implant Biology, School of Dentistry, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece

[2]Department of Operative Dentistry, School of Dentistry, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece

Corresponding Author: Sotiria Davidopoulou, Department of Operative Dentistry, School of Dentistry, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece, Phone: +30 6974642483, e-mail: sdavidop@dent.auth.gr

How to cite this article: Karakostas P, Davidopoulou S, Kalfas S. Use of Hyaluronic Acid in Periodontal Disease Treatment: A Systematic Review. J Contemp Dent Pract 2022;23(3):355–370.

Source of support: Nil

Conflict of interest: None

of gingivitis and periodontitis may improve the clinical outcome. Furthermore, secondary characteristics of the studies were examined to investigate the homogeneity of the studies in terms of treatment modalities and HA formulation used.

Materials and Methods

Selection of Studies

The current systematic review was conducted in accordance with PRISMA guidelines.[15] The focus question was stated as follows: In periodontally diseased subjects (humans), does HA as an adjunct to nonsurgical and/or surgical periodontal therapy results in better clinical periodontal parameters (inflammation, periodontal pocket depth, and clinical attachment level) compared to no treatment, or nonsurgical and/or surgical periodontal therapy.

Inclusion and exclusion criteria were reported following PICOS criteria:

- *Population:* Studies on humans with periodontal disease. (Animal or experimental studies and studies with non-periodontal patients were excluded.)
- *Intervention:* Hyaluronic acid as an adjunct to periodontal therapy. (Trials that had no hyaluronic acid-based intervention were not included.)
- *Comparison:* Periodontal subjects that have not been treated with HA. (Studies without a control group were excluded.)
- *Outcome:* Studies providing clinical dental measurements. (Trials not reporting clinical outcomes were not evaluated.)
- *Study design*: Only randomized controlled clinical trials.

Two authors (Panagiotis and Sotiria) investigated independently and thoroughly in 19 electronic databases from the outset to February 2021. The main search strategy consisted of the Mesh terms "(hyaluronic OR hyaluronate OR hyaluronan) and (periodontal OR periodontally OR periodontics OR periodontitis)". No limits were set as regards demographic characteristics of the trial population, language, or publication date. The whole search strategy is presented in Supplemental Appendix Table 1.

A central electronic database detailing the sourced articles was generated via Mendeley reference management software (© 2020 Mendeley Ltd.). The screening process was managed independently at the title, abstract, and full-text level by the two authors. At each screening step, trials that met the inclusion criteria and studies with missing information were kept till the final full-text evaluation. In case of any dissidence, it was unbruised by discussion. When an agreement was not achieved, a third author was asked to decide (Sotirios). The reasons for studies not meeting the eligibility criteria following the full-text screening level were recorded. All trials fulfilling the eligibility criteria were included and followed by data extraction and risk of bias assessment.

Data Extraction

Clinical variables referring to inflammation of periodontal tissues, periodontal probing depth, and clinical attachment level were set as primary outcomes due to their direct connection to the course of periodontal diseases. In case of different indices used for the same clinical variable among trials, they were grouped per outcome criterion. We designated three main outcome criteria: periodontal inflammation, periodontal pocket depth, and clinical attachment level. Descriptive statistical analysis (counts and percentages) was conducted to summarize the extracted data.

The risk of bias in included studies was evaluated by two reviewers (Panagiotis and Sotiria) with the use of the revised Cochrane risk of bias assessment tool for randomized trials.[16] This tool permits the evaluation of seven separate domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was evaluated as either low risk, high risk, or unclear risk of bias.

Bibliometrics comprises several tools assessing the impact of publications via statistical analyses.[17] The most prevalent tools of this field are topic prominence percentile and field-weighted citation impact, provided by Scopus and the Web of Science database. The first tool aims to reveal the current momentum of a field, and its value derives from weighing three metrics for papers grouped in a field (citation count, scopus views, and average cite score). When the topic prominence percentile takes values over 90, it means that the topic of search is in the current momentum. The second tool calculates how well a publication is cited in comparison to articles of the same topic. The latter goal is achieved by evaluating the year of publication, type of document, and any disciplines related to its source. Values that surpass 1.00 represent an article that has been cited more than expected compared to the average.

Moreover, all information as regards adverse events related to the use of HA, if any, were reported and evaluated.

Results

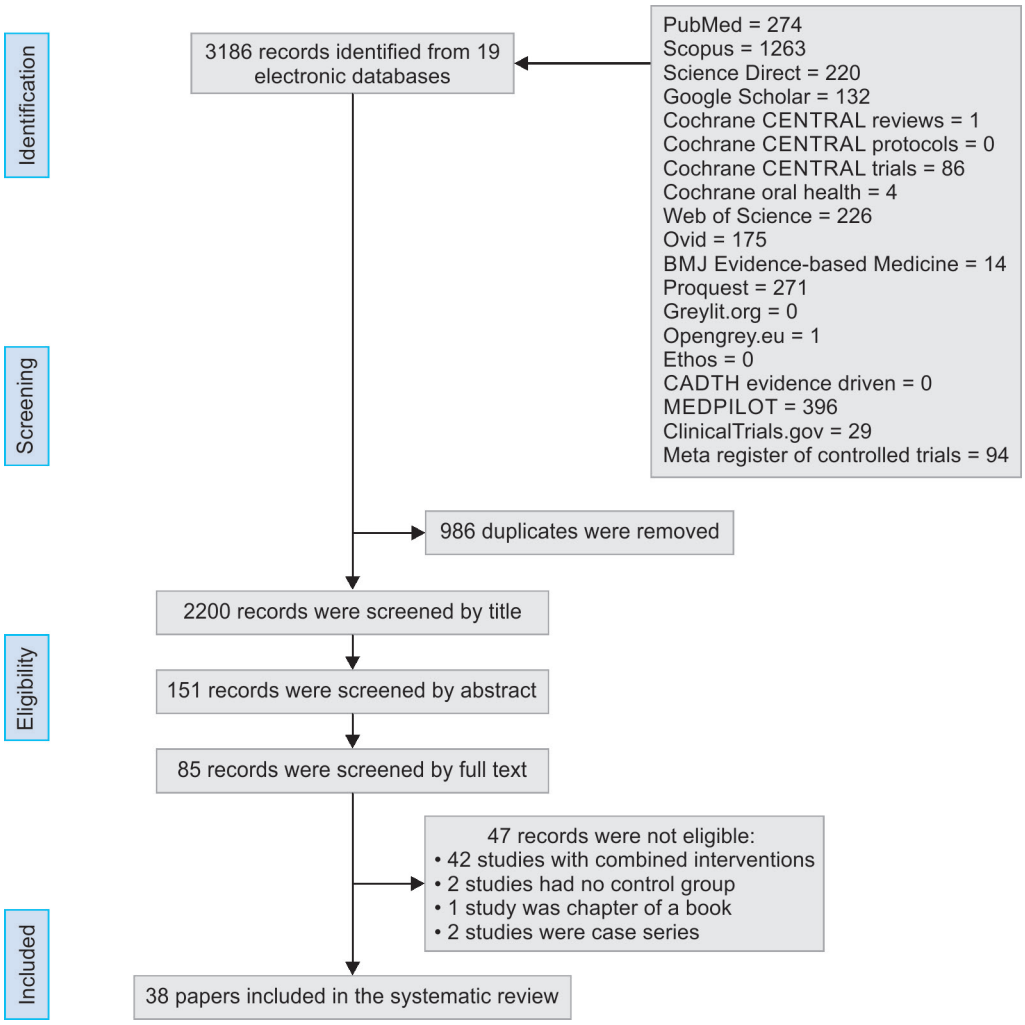
This review of 19 electronic databases led initially in 3,186 papers (Flowchart 1). Following duplicates removal, 2,200 publications were screened by title. In the next step of the assessment, 151 articles were evaluated at the abstract level, while only 85 trials met the criteria to be assessed by full text. In total, 47 studies were removed by full-text screening for not meeting the eligibility criteria. Last but not the least, 38 randomized controlled clinical trials were selected, and their main characteristics are presented in Table 1.[18–55] Eight studies were related to gingivitis therapy, 20 studies were referred to nonsurgical periodontal treatment, and 10 studies to surgical periodontal therapy. Among surgical modalities, most trials were referred to open flap debridement (7 trials), followed by coronally advanced flap technique (2 trials), and gingivectomy (1 trial).

The outcomes of the systematic review were categorized as primary, which were those that answered the focus question, and secondary regarding additional quality characteristics of the included studies.

Primary Outcomes

Three were the main clinical variables evaluated in the included studies: (a) inflammation of periodontal tissues, (b) depth of periodontal pockets, and (c) clinical attachment level. More specifically, a great range of different indices was applied for evaluating each main clinical variable. Regarding inflammation of periodontal tissues, the following indices were applied: bleeding on probing, papilla bleeding index, sulcus bleeding index, bleeding index, gingival index, and modified gingival index.[2,56] Regarding the depth of the periodontal pocket, two indices were applied: probing pocket depth (PPD) and pocket depth (PD). Indices used to assess attachment level were: clinical attachment level, probing attachment level, relative attachment level, recession, gingival recession, gingival recession height, recession depth,

Flowchart 1: Flowchart of studies selection according to PRISMA guidelines



recession reduction, and localization of the gingival margin.[7,57] The positive effect of adjunct HA on each of the main clinical variables, confirmed statistically, per therapy category, for all studies included is presented in Figure 1. Moreover, the overall effect, as it was claimed and concluded by the authors for each study is presented in Figure 1. In the gingivitis group, one study also included clinical attachment level as an outcome criterion, and in two studies, a significant effect of HA on periodontal inflammation was not detected. Albeit, all authors in this group claimed a positive overall effect of HA. Regarding the studies in the nonsurgical group, a significant positive effect was reported mainly on periodontal inflammation and pocket depth and only in a few studies on clinical attachment level. Nevertheless, the authors in most of these trials concluded that the use of HA presents an overall positive effect. Finally, while most of the surgical group trials failed to present significant positive effects in any of the primary outcome criteria, eight out of ten studies concluded that HA presents an overall positive effect. No side effects were reported in any of the included studies.

Secondary Outcomes

Engström et al.[26] were the first who investigated the adjunct use of HA in periodontal therapy. Since then, a few more studies were published until 2008, and ever since an increasing number of randomized clinical trials were published. 2019 was the year with the most publications in this scientific field.

Various HA compounds were tested. In the majority of the trials, HA was used in gel form, in some studies, by a mouthwash or spray, and in one study by fibers. The commercial products used were also different (Table 2). The HA concentrations ranged from 0.2 to 0.8% in gel and mouthwash products, whereas a much lower concentration (0.025%) was preferred in the HA spray. All except for two products contained HA with high molecular weight varying from 10^5 to 10^6 Da. No information was provided regarding the molecular weight of HA in one product. Heterogeneity was also detected regarding the chemical HA compound used in each product. Sodium hyaluronate and ester of HA with benzyl alcohol were mostly selected, while one product used a polycarbophil-based HA gel.

Most of the studies reported the tooth site as the search unit, whereas merely a small number of trials reported the human as the search unit. Publications were originated mostly from Asia, followed by Europe. On a country level, the majority of surveys were conducted in India (14 trials) and in Italy (6 trials).

Other features of these studies are presented in Figure 2. Over 20 trials showed to have an open access status, while less than 10

Table 1: Main characteristics of the studies included in the systematic review

	Author (year) (place of study)	*Study design*	*Sample*	*Intervention*	*Follow-up*	*Outcome criteria*	*Results*	*Conclusions*	*Limitations as stated by authors*
Gingivitis therapy									
1	Jentsch et al. (2003)[18] (Germany)	RCT	50 male pts (25 with 0.2% HA and 25 with placebo gel)	1 mL of the gel on the inflamed buccal gingiva	3 weeks	API, TPI, PBI	PI: sig. improvement for the HA group from day 4 BI: sig. improvement for the HA group from day 7	Beneficial effect in plaque-induced gingivitis	Not reported
2	Pistorius et al. (2005)[19] (Germany)	RCT	60 pts. (40 with HA and 20 without HA)	HA spray in the HA group for 7 days while no placebo for the control group	7 days	API, SBI, PBI	SBI: decrease for the test group at day 3 and day 7 PBI: sig. improvement for the test group	Potential useful adjunct to gingivitis	Uncertain if the long-term use leads in side effects in the oral mucosa
3	Rodrigeus et al. (2010)[20] (India)	RCR	45 pts. (15 with HA rinse, 15 with CHX rinse, 15 with water-based rinse)	Mouthrinse twice daily for 1 minute without mechanical oral hygiene	4 days	PI, SBI	PI: the water-based group had the lowest improvement while the CHX group showed a slightly bigger reduction in PI than the HA group SBI: no stat. difference among groups	Significant beneficial effect	Short-time frame of study, xylitol used as a preservative may have anti-plaque action, parallel design could have affected the results
4	Sapna et al. (2011)[21] (India)	RCT	28 pts. (1st QR only scaling, 2nd QR scaling and topical HA gel, 3rd QR only topical HA gel, 4th QR topical and intrasulcular HA gel)	In the first 3 weeks, the scaling was done, and in the following 3 weeks, the different HA were made	6 weeks	PI, GI, GBI	PI, GI, and GBI: sig. improvement among all groups Topical and intrasulcular HA seemed to be equivalent to scaling, whereas only topical HA showed the smallest effect	Local beneficial effect	The complicated study design
5	Sahayata et al. (2014)[22] (India)	RCT	105 pts. (35 negative control group, 35 placebo control group, 35 test group)	Negative control group: only scaling Placebo control group: scaling and placebo gel twice daily for 4 weeks Test group: scaling and 0.2% HA gel twice daily for 4 weeks	4 weeks	API, GI, PBI	GI and PBI showed sig. improvement in the test group compared to the other groups at 4 weeks	Significant beneficial effect	Small sample size, a short evaluation period
6	Gizligoz et al. (2019)[23] (Turkey)	RCT	33 pts. (3 sequence treatments for each one: 0.2% CHX mouthwash, 0.025% HA mouthwash, distilled water, only one of them in each time period)	Twice daily for 4 days with 10 days of wash out before the next mouthwash	39 days	PI, mGI, GCF, questionnaire	PI: sig. reduction for CHX followed by HA MGI and GCF: no sig. differences between CHX and HA Questionnaire: better taste, less sensitivity, burning sensation, mouth dryness, and numbness perception for HA compared to the other two mouthwashes	Better acceptance from patients as an adjunct compared to chlorhexidine	Short-term evaluation period

7	Al-Shabeeb et al. (2019)[24] (Iraq)	RCT (split-mouth)	25 pts. (left side of maxilla only scaling, right side of maxilla scaling and HA gel)	Three times daily application of 0.2% HA gel in the half of the mouth	1 week	PI, PBI, GI	Both sides revealed sig. differences in all indices measured, but the improvement was bigger for the right side	Beneficial effect in gingivitis	Not reported
8	Abdulkareem et al. (2020)[25] (Iraq)	RCT (parallel design)	80 pts. (20 0.12% CHX, 20 distilled water, 20 0.025% HA, 20 water-based antioxidant)	Twice daily after brushing teeth	1 week	PI, BOP, questionnaire	PI: sig. decrease for all groups but CHX showed sig. difference compared to other groups BOP: all groups led in sig. reduction Questionnaire: shade changes with all and pts. preferred HA	Beneficial in bleeding reduction, better acceptance by the participants	Short evaluation period, cases without severe inflammation
Nonsurgical periodontal therapy									
9	Engstrom et al. (2001)[26] (Sweeden)	RCT (split-mouth)	9 pts.	Control site: SRP Test site: SRP + HA (3 times with 1-week interval)	12 months	PD, PI, BOP, BH	BH: no sig. difference between 2 sites at 12 months PD, PI, BOP: all were reduced in both sites without sig. difference at 12 months	No significant influence of HA (in contact to bone and soft tissue) to immune system	Not reported
10	Xu et al. (2004)[27] (Germany)	RCT (split-mouth)	20 pts.	Control site: SRP Test site: SRP + 0.2% HA weekly for 6 weeks (7 applications)	12 weeks	BOP, PD, CAL	PD, CAL, BOP: sig. change for both groups whereas no sig. difference between 2 groups for all parameters at 12 weeks	Beneficial effect only in reduction of sulcus fluid flow rate	Not reported
11	Johannsen et al. (2009)[28] (Sweeden)	RCT (split-mouth)	12 pts.	Control site: SRP Test site: SRP + 0.2% HA gel	12 weeks	BOP, PD, CAL	BOP, PD, CAL: all parameters were improved for both groups, whereas there was no sig. difference between groups at 12 weeks	Beneficial effect	Not reported
12	Pilloni et al. (2011)[29] (Italy)	RCT (split-mouth)	19 pts.	Control site: OH Test site: OH + HA gel daily	3 weeks	PI, GI, BOP, PD, PAL	PPD, GI, BOP: sig. greater reduction for the test group compared to the control group PLI, PAL: no sig. difference between the two groups	Beneficial effect	Not reported
13	Koshal et al. (2012)[30] (United Kingdom)	RCT (split-mouth)	52 pts.	Control site: SRP + placebo Test site: SRP + 0.8% HA gel (single application)	3 months	PD, BOP	PD, BOP: sig. greater improvement for the test group compared to the control group	Beneficial effect	Not reported
14	Gontiya et al. (2012)[31] (India)	RCT	26 pts. (120 sites)	Control group (60 sites): SRP Test group (60 sites): SRP + 0.2% HA gel (BL, 1st, 2nd, 3rd week)	12 weeks	PI, GI, BI, PD, RAL	BI, GI: sig. difference in favor of test group at 12 weeks PD, RAL: no sig. difference between groups at 12 weeks Intragroup analysis: all parameters showed sig. change at 12 weeks and the improvements were higher for the test group		Not reported

(Contd...)

Table 1: *(Contd...)*

Author (year) (place of study)		*Study design*	*Sample*	*Intervention*	*Follow-up*	*Outcome criteria*	*Results*	*Conclusions*	*Limitations as stated by authors*
15	Bevilacqua et al. (2012)[32] (Italy)	RCT (split-mouth)	11 pts.	Control group: SRP + placebo gel Test group: SRP + HA gel	Control: 45 days Test: 90 days	API, BOP, CAL, PPD	PPD, BOP: sig. change for both groups at 45 days API, CAL: no sig. differences	Beneficial effect	Not reported
16	Chauhan et al (2013)[33] (India)	RCT	60 pts. (20 pts. in each group)	Group I (control): SRP Group II: SRP + HA gel Group III: SRP + CHX gel	3 months	PI, GI, PPD, CAL	PPD, CAL: greater change in group I compared to group II at 3 months	Beneficial effect	Results can be used only as preliminary data
17	Eick et al. (2013)[34] (Germany)	RCT	34 pts. (17 pts. in each group)	Control group: SRP Test group: SRP + HA gel + HA rinse twice daily for 2 weeks	6 months	PI, BOP, PD, CAL	PD and CAL: sig. decreased in both groups. PD and reduction of the number of pockets with PD ‡5 mm: sig. higher in the test group after 6 months CAL, BOP and PI: no difference between groups at 6 months	Potential beneficial effect	Not reported
18	Rajan et al. (2014)[35] (India)	RCT (split-mouth)	33 pts.	Control group: SRP Test group: SRP + 0.2% HA gel (after SRP and 1 week after)	12 weeks	GI, PI, BOP, PPD, CAL	BOP: sig. decrease in both groups at 12 weeks while the test group showed greater reduction PI, GI, PPD: sig. reduction for both groups at 12 weeks CAL: sig. difference between the groups at 12 weeks	Beneficial effect	Not reported
19	Polepalle et al. (2105)[36] (India)	RCT (split-mouth)	18 pts.	Control group: SRP Test group: SRP + 0.8% HA gel (after SRP and 1 week after)	12 weeks	GI, PI, PPD, RAL	PI, BOP, PD and RAL: sig. greater improvement for the test group at 12 weeks	Significant beneficial effect	Small sample, short evaluation period
20	Sharma et al. (2016)[37] (India)	RCT (split-mouth)	24 pts.	Group A: SRP + coenzyme Q10 gel Group B: SRP + 0.8% HA gel Group C: SRP	6 weeks	PI, BI, PD, CAL	PI, EIBI, PD and CAL: no sig. difference among groups at 6 weeks whereas in intragroup comparison all groups showed sig. changes regarding all parameters at 6 weeks	Beneficial effect	Not reported
21	Shah et al. (2016)[38] (India)	RCT (split-mouth)	9 pts.	Control group: SRP Test group: SRP + 0.8% HA gel	12 weeks	PI, GI, PD, RAL	PI and GI: no sig. difference between groups at 12 weeks PPD and RAL: sig. improvement for test group compared to control group at 12 weeks	Beneficial effect	Not reported
22	Malikarjun et al. (2016)[39] (India)	RCT (split-mouth)	20 pts.	Control group: SRP Test group: SRP + 0.2% HA gel	6 weeks	PI, GI, PPD, RAL	PI, GI, PPD, RAL: no sig. difference between groups at 6 weeks while there was sig. improvement within each group from BL at 6 weeks	Beneficial effect	Not reported

23	Omer et al. (2018)[40] (Sweden)	RCT	33 pts.	Control group (17 pts): SRP Test group (16 pts): SRP + 0.2% HA gel	6 weeks	PI, GI, PPD, CAL	Test group: sig. change in PPD and CAL at 6 weeks Control group: no sig. change in PPD and CAL at 6 weeks	Beneficial effect	Not reported
24	Al-Shammari et al .(2018)[41] (Saudi Arabia)	RCT (split-mouth)	24 pts.	Control group: SRP Test group: SRP + 0.8% HA gel	12 weeks	PI, GI, PBI, PPD, CAL	PI, GI, PBI, PPD, and CAL: showed decrease at 12 weeks in both groups. Moreover, all parameters except for CAL were sig. reduced in test compared to control group at 12 weeks	Beneficial effect	Not reported
25	Lobato et al. (2019)[42] (Portugal)	RCT (split-mouth)	16 pts.	Control group: SRP Test group: SRP + 0.8% HA gel (single application)	6 and 12 weeks	PI, GI, BOP, PD, CAL	Both groups: sig. improvement of PI, GI, BOP, PD, CAL after 12 weeks Test group: sig. different BOP compared with the control test, whereas no sig. difference as regards PD and CAL	Beneficial effect	Short evaluation period, single application of hyaluronic acid
26	Mahmood et al. (2019)[43] (Iraq)	RCT	30 pts. (10 pts in each group)	Group I: RSD + 0.2% HA gel Group II: RSD + MTZ gel Group III: RSD G1 and G2: Initially the gel was set intrasulcularly and then applied supragingivally twice daily	1 week	PI, GI, PPD	Intragroup analysis: PI, GI, PPD revealed high sig. changes between BL and 1 week Intergroup analysis: sig. changes for GI and high sig. changes for PPD, while no sig. changes for PI	Beneficial effect	Not reported
27	Ibraheem et al. (2020)[44] (Iraq)	RCT	20 pts. (10 pts. in each group)	Group I (10 pts.): SRP + 0.8% HA gel Group II (10 pts.): SRP	4 weeks	PLI, GI, BOP	Group I: highly sig. difference for BOP and no sig. difference for PLI and GI between the 2nd and 3rd visit Group II: highly sig. difference for GI and sig. for PLI and BOP between the 2nd and 3rd visit Intergroup comparison: highly sig. difference in 1st visit for PLI and BOP in 3rd visit.	Beneficial effect	Not reported
28	Aydinyurt et al. (2020)[45] (Turkey)	RCT	24 pts. (6 pts. in each group)	Group I: SRP + saline Group II: SRP + HA gel Group III : SRP + HA mouthrinse Group IV: SRP + HA mouthrinse + A gel	4 weeks	PI, GI, BOP, PD, GRH, CAL, LGM	PI, GI, BOP, PD, GRH, CAL, LGM: sig. improvement in all groups	No beneficial effect	Short evaluation period, lack of microbiological evaluation and comparison of doses and application differences

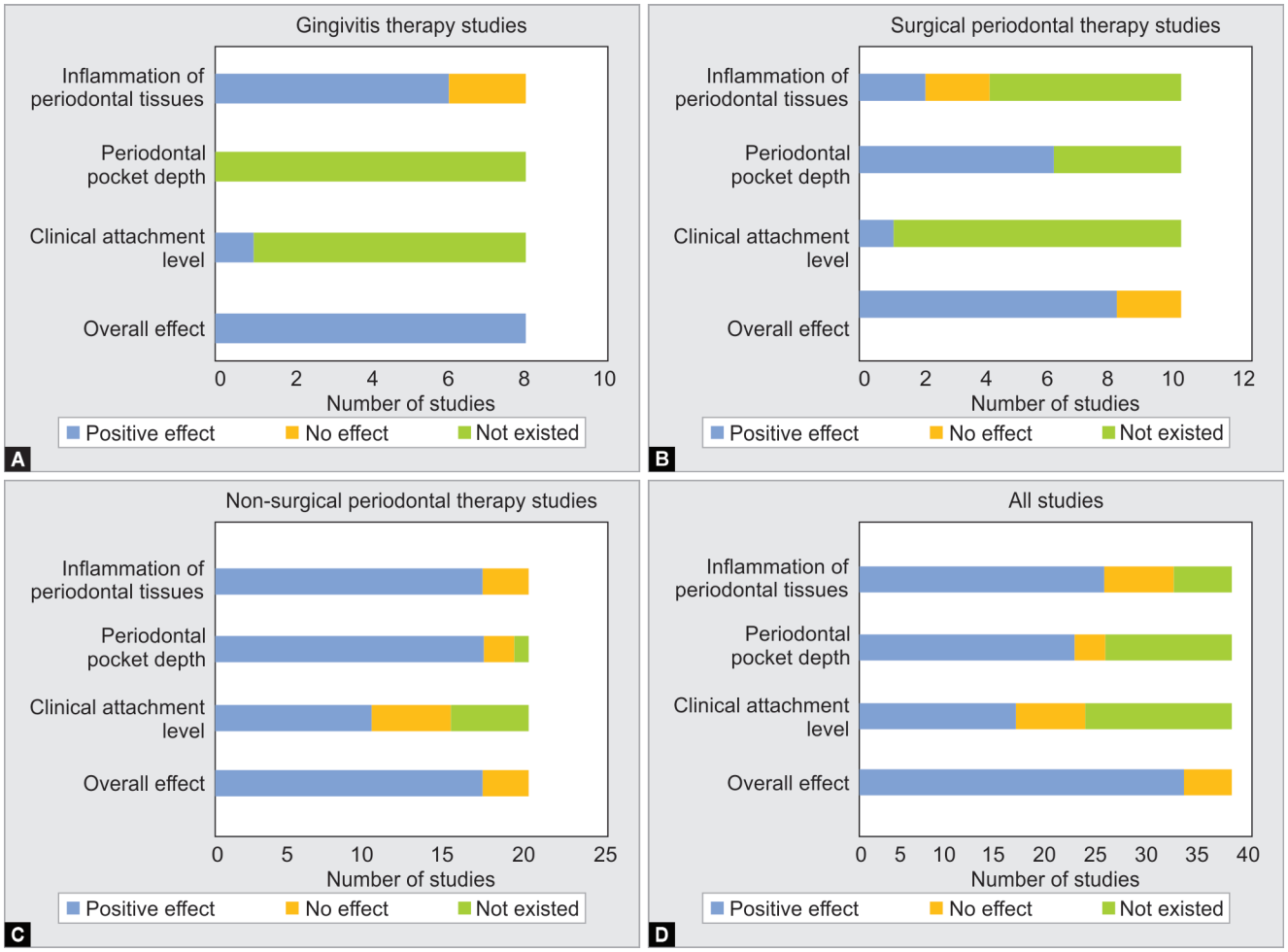
(Contd...)

Table 1: *(Contd...)*

	Author (year) (place of study)	*Study design*	*Sample*	*Intervention*	*Follow-up*	*Outcome criteria*	*Results*	*Conclusions*	*Limitations as stated by authors*
Surgical periodontal therapy									
29	Galli et al. (2008)[46] (Italy)	RCT	72 pts. (36 with 0.8% HA and 36 with placebo)	Single application after suturing for 2 minutes	10 days	Wound healing, Adverse events, post-operative complications	Wound healing: no sig. difference between the groups No post-operative complications or adverse events were recorded	No beneficial effect	Study design
30	Fawzy El-Sayed et al. (2012)[47] (Egypt)	RCT (split-mouth)	14 pts. (control MWF and placebo gel and test MWF and 0.8% HA gel)	Initially SRP and after 8 weeks 2 pairs of premolars and molars received MWF + placebo or MWF + HA	3 and 6 months	PD, CAL, GR, PI, GI, BOP	Test group: sig. greater gain in CAL and sig. more reduction in GR compared to control group in 3 and 6 months. No sig. differences as regards PD, PI, BOP Both groups showed sig. improvement in CAL, PD, PI, BOP	Beneficial effect	Not reported
31	Briguglio et al. (2013)[48] (Italy)	RCT	40 pts. (20 OFD + EDTA and 20 OFD + EDTA + HA fibers)	Initially SRP, and the remaining infrabony defects scheduled for OFD with or without HA	12 and 24 months	PI, BOP, CAL, PD	Test group: sig. greater gain in CAL and sig. more reduction in PD compared to control group at 12 and 24 months PI and BOP: no sig. differences but their values decreased in both groups at 12 and 24 months	Beneficial effect	Not reported
32	Kumar et al. (2014)[49] (India)	RCT (split-mouth)	10 pts./20 Miller I defects (10 defects CAF and 10 defects CAF + HA gel)	CAF with or without 0.2% HA gel	6 months	RD, PPD, CAL	Both groups showed sig. differences as regards RD, PPD, CAL compared to baseline, whereas there was no sig. difference between the groups at any parameter Clinically, test group seemed to be more stable at 6 months	Beneficial effect	Small sample, low statistical power, no histological evaluation
33	Gupta et al. (2017)[50] (India)	RCT (split-mouth)	10 pts./20 sites with furcation GRADE II	Group A: OFD + 0.8% HA Group B: OFD	6 months	PI, GI, BI, PPD, RAL	PI, GI, BI, PPD, RAL, horizontal and vertical component: sig. difference for both groups from baseline to 6 months Gingival margin position: no sig. difference for both groups from baseline to 6 months No sig. differences between the 2 groups at any parameter	Beneficial effect	Small sample, short evaluation period, no histological evaluation

34	Pilloni et al. (2019)[51] (Italy)	RCT	30 pts. with Miller I recession	Control group: CAF Test group: CAF + cross-link HA	18 months	RR, CAL-gain, PPD, KT, CRC, MRC, post-operative morbidity	RR: sig. higher in the test group PPD: sig. increased in both groups KT gain: no sig. difference between groups CRC: sig. higher % for the test group MRC: sig. higher for test group Swelling and discomfort: sig. lower values for the test group Pain intensity: no sig. difference between groups	Beneficial effect	Small sample, low quality of patients' morbidity evaluation, study had not split-mouth design
35	Reddy et al. (2019)[52] (Pakistan)	RCT	30 pts. (Group A: LLT, Group B: 0.2% HA gel, Group C: Herbal gel)	For each group: application 1st, 3rd, 7th day after gingivectomy	6 weeks	PI, GI, GEI, pain perception	PI, GI, GEI: sig. improvement within the groups. On intergroup comparison, GEI revealed sig. differences only for Group A Pain perception: the least for Group A	Slight beneficial effect	Small sample
36	Marwa et al. (2020)[53] (Egypt)	RCT	16 pts/20 intrabony defects	FLAP + 0.8% HA or FLAP + PRF or FLAP + 0.8% HA + PRF or FLAP only	3 and 6 months	PPD, CAL, GI, PI	PI, GI, PPD and CAL: no sig. difference among groups while there was sig. improvement for each group in different time point	Beneficial effect	Not reported
37	Pilloni et al. (2021)[54] (Italy)	RCT	32 pts./32 defects	Test group: 0.2% HA + SFA Control group: EMD + SFA	12, 18 and 24 months	CAL, PD, REC, BOP	At 24 months both groups resulted in sig. PD reduction and CAL gain, while only PD reduction was found sig. higher for the control group compared to test group REC: slightly lower for test group BOP: no sig. difference between groups	Beneficial effect	Absence of radiographic bone fill as an outcome parameter
38	Mamajiwala et al. (2021)[55] (India)	RCT	20 pts/40 bilateral intrabony defects (20 defects in each group)	Test group: 0.8% HA gel + OFD Control group: OFD + placebo gel	6 and 12 months	PI, GI, PD, CAL, GR. DF, ACC, DR	After 12 months, the test group showed sig. greater CAL gain, DF, and mean PD reduction compared to the control group The control group sig. increases in GR compared to the test group after 12 months	Potential beneficial effect	Only contained defects included, practically impossible to include only defects with similar morphology regarding mesiodistal and buccolingual dimension, grade I and II furcation defects might have influenced the regenerative outcome, possible washout of hyaluronic acid in gel form, no histological evaluation

ACC, alveolar crest changes; API, approximal plaque index; BH, bone height; BI, bleeding index; BOP, bleeding on probing; CAL, clinical attachment level; CRC, complete root coverage; DF, bone defect fill; DR, defect resolution; GEI, gingival enlargement index; GI, gingival index; GR, gingival recession; GRH, gingival recession height; KT, keratinized tissues; LGM, localization of the gingival margin; mGI, modified gingival index; MRC, mean root coverage; PAL, probing attachment level; PBI, papilla bleeding index; PD, pocket depth; PI, plaque index; PPD, probing pocket depth; RAL, relative attachment level; RD, recession depth; REC, recession; RR, recession reduction; SBI, sulcus bleeding index; TPI, Turesky plaque index



Figs 1A to D: Main outcomes of the studies included in the systematic review. Significant effect of hyaluronic acid for each main clinical variable examined per therapy category and overall effect, as it is claimed by authors, for all studies included: (A) Gingivitis therapy, (B) Nonsurgical periodontal therapy, (C) Surgical periodontal therapy, and (D) All studies included

Table 2: Main features of each hyaluronic acid-based commercial product used in the included studies

Brand name	*Substance*	*Molecular weight*	*Company*
AFTA MED	Gel Polycarbophil/hyaluronic acid	High	Bioplax Limited (Wallington, United Kingdom)
Aminogam	Gel Sodium hyaluronate	NR	Errekappa Euroterapici (Spa, Italy)
Gengigel	Gel 0.2 or 0.8% Mouthwash 0.025% Spray 0.01% Sodium hyaluronate	High 1–1.8 × 10^6 Da	Ricerfarma (Milan, Italy)
Healon GV	Gel 1.8% Sodium hyaluronate	High 3.2 × 10^5 Da	Pharmacia and Upjohn (Uppsala, Sweden)
HyaDENT BG	Gel 2 mg Hyaluronic acid and 16 mg hyaluronic acid per syringe	High	BioScience (Dümmer, Germany)
HYAFF	Gel Ester of hyaluronic acid with benzyl alcohol	Low 5–7.3 × 10^5 Da	Anika Therapeutics (Bedford, USA)
Hyaloss Matrix	Fibers Ester of hyaluronic acid with benzyl alcohol	Low 5–7.3 × 10^5 Da	Meta G.C.M. (Reggio Emilia, Italy)

Fig. 2: Secondary characteristics of the studies included in the systematic review

trials reported funding for their surveys. Regarding blinding of each research, merely 8 trials proceeded in a double-blind design. The most popular brand name, among commercial products used, turned out to be "GENGIGEL". Nevertheless, over the half studies reported one or two recall visits, and the prevalent time period of follow-up was up to 3 months. Regarding bibliometrics, topic prominence percentile values surpassed 90 only in two articles, whereas the prevalent value was 41.031, and it was detected in 15 studies. Regarding field-weighted citation impact, merely six articles were given values over 1.00.

Risk of Bias Evaluation

The risk of bias was evaluated for each trial by assessing each domain separately (Table 3). Figure 3 presents risk of bias level of each domain per treatment modality and overall. In all publications included, neither selective reporting nor incomplete data or other bias were detected. In the case of gingivitis therapy, few trials reported unclear data regarding random sequence generation and allocation concealment. The domains related to blinding of participants and personnel and outcome assessment were characterized with a high risk of bias for the majority of all clinical trials included in this systematic review. At the level of overall bias, merely two trials from gingivitis therapy, one trial from nonsurgical periodontal therapy, and six trials from surgical periodontal therapy were reported being of low risk of bias.

Interconnection/Interaction between Primary and Secondary Outcomes

Descriptive statistical analysis of secondary characteristics and primary outcomes of the included studies revealed some interesting interconnections. Studies that were published with open access status presented better results regarding inflammation of periodontal tissues, while studies that have received funding did not. Maximum reduced inflammation was also detected when HA was applied in gel form compared to other forms, as well as in 3-month recalls. An association between depth of periodontal pocket and duration of follow-up was also detected, with best results at 3-month follow-ups. Nevertheless, this parameter was found to be independent of the journal status (open access or not), funding of the survey, and the unit of search (patient or tooth). Clinical attachment level values were found to be improved when checked in 3 months posttreatment, and when the trials were funded. However, it seemed to be irrespective of the status of the journal or the unit of search.

Tables 3A to C: Risk of bias of included studies in: (A) Gingivitis therapy, (B) Nonsurgical periodontal therapy, and (C) Surgical periodontal therapy [(+): low risk of bias; (-): high risk of bias; (?): unclear risk of bias)]

Table 3A: Gingivitis therapy

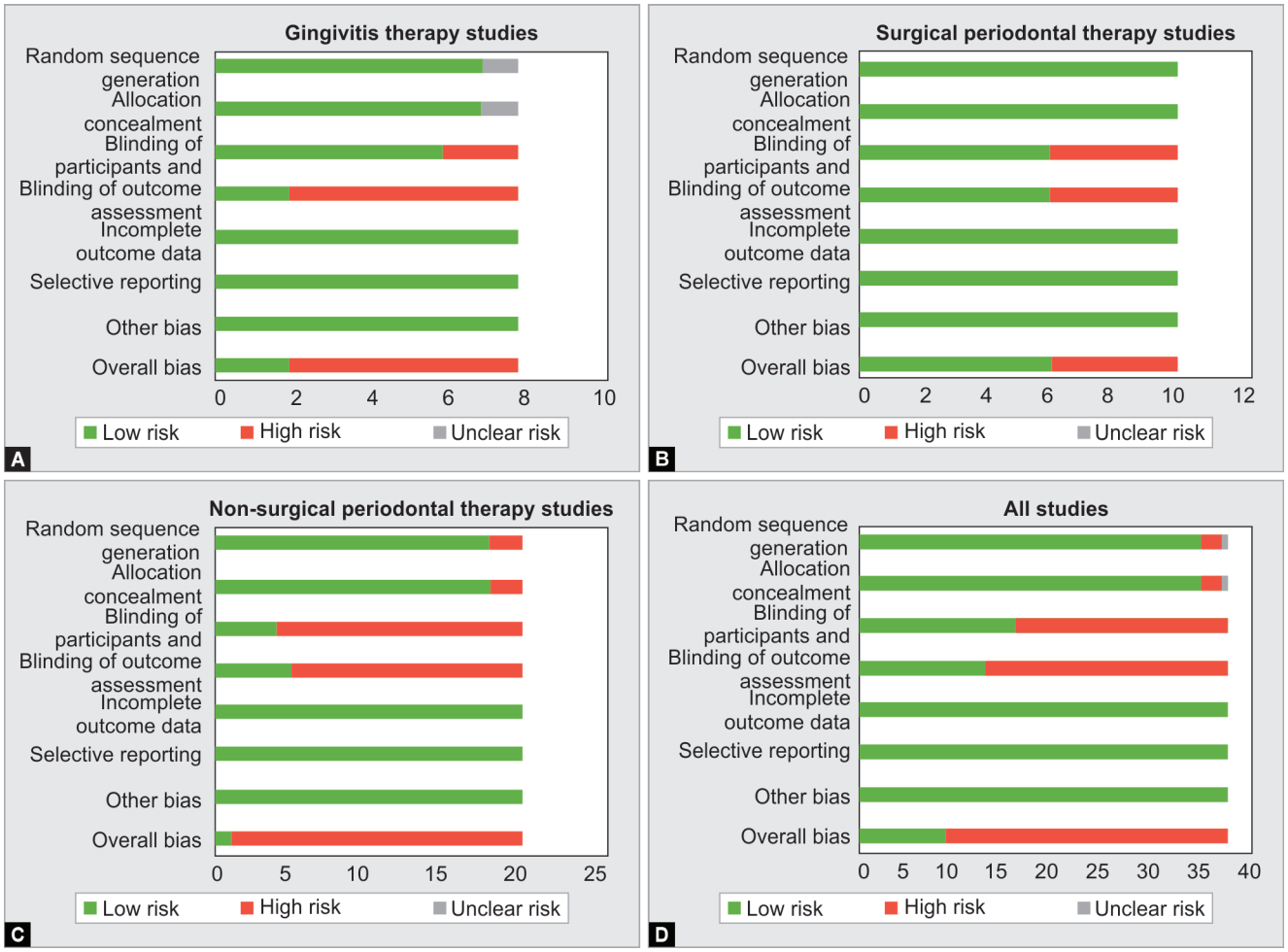
Author (year)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*	*Overall bias*
Jentsch et al. (2003)[18]	+	+	+	-	+	+	+	-
Pistorius et al. (2005)[19]	+	+	+	+	+	+	+	+
Rodrigeus et al. (2010)[20]	+	+	-	-	+	+	+	-
Sapna et al. (2011)[21]	+	+	+	-	+	+	+	-
Sahayata et al. (2014)[22]	+	+	+	-	+	+	+	-
Gizligoz et al. (2019)[23]	+	+	+	-	+	+	+	-
Al-Shabeeb et al. (2019)[24]	?	?	-	-	+	+	+	-
Abdulkareem et al. (2020)[25]	+	+	+	+	+	+	+	+

Table 3B: Nonsurgical periodontal therapy

Author (year)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*	*Overall bias*
Engström et al. (2001)[26]	+	+	-	+	+	+	+	-
Xu et al. (2004)[27]	-	-	-	-	+	+	+	-
Johannsen et al. (2009)[28]	+	+	-	-	+	+	+	-
Pilloni et al. (2011)[29]	+	+	-	-	+	+	+	-
Koshal et al. (2012)[30]	+	+	+	-	+	+	+	-
Gontiya et al. (2012)[31]	+	+	-	-	+	+	+	-
Bevilacqua et al. (2012)[32]	+	+	+	-	+	+	+	-
Chauhan et al. (2013)[33]	+	+	-	-	+	+	+	-
Eick et al. (2013)[34]	+	+	-	+	+	+	+	-
Rajan et al. (2014)[35]	+	+	-	-	+	+	+	-
Polepalle et al. (2105)[36]	+	+	-	-	+	+	+	-
Sharma et al. (2016)[37]	+	+	-	+	+	+	+	-
Shah et al. (2016)[38]	+	+	-	-	+	+	+	-
Malikarjun et al. (2016)[39]	+	+	-	-	+	+	+	-
Omer et al. (2018)[40]	+	+	+	+	+	+	+	+
Al-Shammari et al. (2018)[41]	+	+	-	-	+	+	+	-
Lobato et al. (2019)[42]	+	+	-	+	+	+	+	-
Mahmood et al. (2019)[43]	+	+	-	-	+	+	+	-
Ibraheem et al. (2020)[44]	-	-	-	-	+	+	+	-
Aydinyurt et al. (2020)[45]	+	+	+	-	+	+	+	-

Table 3C: Surgical periodontal therapy

Author (year)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*	*Overall bias*
Galli et al. (2008)[46]	+	+	+	+	+	+	+	+
Fawzy El-Sayed et al. (2012)[47]	+	+	+	+	+	+	+	+
Briguglio et al. (2013)[48]	+	+	+	+	+	+	+	+
Kumar et al. (2014)[49]	+	+	-	-	+	+	+	-
Gupta et al. (2017)[50]	+	+	-	-	+	+	+	-
Pilloni et al. (2019)[51]	+	+	+	+	+	+	+	+
Reddy et al. (2019)[52]	+	+	-	-	+	+	+	-
Marwa et al. (2020)[53]	+	+	-	-	+	+	+	-
Pilloni et al. (2021)[54]	+	+	+	+	+	+	+	+
Mamajiwala et al. (2021)[55]	+	+	+	+	+	+	+	+



Figs 3A to D: Risk of bias evaluated per therapy category and overall risk of bias of all studies included according to Cochrane Handbook guidelines: (A) Gingivitis therapy, (B) Nonsurgical periodontal therapy, (C) Surgical periodontal therapy, and (D) All studies included

Discussion

The current systematic review as regards the local application of HA in the management of gingivitis and periodontitis, finally resulted in the inclusion of 38 randomized clinical trials. Compared to previous reviews, the present number of included studies is greater due to the number of electronic databases covered and the absence of year or language limitations. A considerable variation was observed in reported results per main clinical variable examined. In 25 studies, statistically significant effect of HA application was found regarding periodontal inflammation rather than the other two main clinical variables, i.e., periodontal probing depth and clinical attachment level. Interestingly, some authors claimed an overall positive effect, probably based on the trend of improvement, even though no significant difference was observed for any of the main outcomes. Furthermore, data regarding side effects or complications after the adjunct use of HA was given in only one study that examined possible adverse events and postoperative complications related to the topical use of HA during oral surgeries, and they concluded that no complications or adverse events were recorded.[46] Additionally, there was no report of any tested concentration being toxic for humans. From all the data above, it can be concluded that the application of HA as an adjunct agent is a treatment modality characterized by safety.

In more detail, regarding the adjunct use of HA in gingivitis therapy, the study of Pistorius et al., which was characterized by low risk of bias, reported a significant decrease in periodontal inflammation both in 3 and 7 days.[19] Moreover, Abdulkareem et al. study which was also assessed as low risk of bias, concluded that even though the use of chlorhexidine and HA led in comparable reduction in bleeding on probing, all patients preferred HA due to shade changes of chlorhexidine.[25] In addition, the only study that was assessed as low risk of bias in the group of nonsurgical periodontal therapy, was the study of Omer et al., which concluded that the combined SRP with 0.2% HA gel improved significantly the PPD and CAL indices at 6 weeks postoperatively.[40] In the surgical group, 5 out of 7 trials testing open flap debridement (with or without HA) were assessed as low risk of bias. A significant improvement in PD reduction and CAL gain in 3 and 6 months and in 12 and 24 months were reported.[47,48] In agreement, the results of Pilloni et al. reported a significant PD reduction and CAL gain at 24 months, and in addition, they showed a slightly lower postoperative recession in the HA group (0.2% gel) in accordance with the results of Fawzy El-Sayed et al. that tested 0.8% HA gel.[47,54] Mamajiwala et al. tested 0.8% HA gel during open flap debridement in bilateral intrabony defects and concluded that the HA group showed a significantly greater CAL gain, defect fill, and mean PD

reduction compared to the control group after 12 months.[55] The only one trial testing gingivectomy was evaluated with a high risk of bias and concluded that the adjunct use of 0.2% HA gel may improve periodontal inflammation in 6 weeks since they have observed a clinical improvement without statistical significance.[52] The clinical trial of Pilloni et al. regarding coronally advanced flap (with or without HA) that was assessed as low risk of bias concluded that significant higher recession reduction and a significant higher percentage of complete root coverage were observed after the adjunct application of crosslink HA.[51]

Regarding the secondary characteristics of the included studies, the systematic review revealed great variance in HA concentrations (0.0025 or 0.2 or 0.8%), forms of application (gel, mouthwash, etc.), application frequencies, and follow-up intervals. A great variation of the sample size and observation unit among studies was also noticed, and in only 14 studies a placebo regimen was given in the control groups. The fact that most of the trials were conducted in Asia may be associated with the possible difficulties in getting ethical approval to conduct randomized clinical trials among different countries and regiments. A thorough record of the ingredients in the different commercial products used in the included trials revealed a large heterogeneity. Differences in the chemical type and molecular weight of the HA applied raise considerations on comparability of results. As a result, the determination of an optimal HA application form (concentration molecular weight) and frequency was hindered due to differences in study design among the selected studies. Regarding the design of the trials included in the current systematic review, 17 randomized clinical trials followed a split-mouth design. This model led in less patients needed for each research because split-mouth trials have as observation unit the site and not the subject. The main purpose of the split-mouth design is to remove all components related to differences between subjects from the treatment comparisons. By making within-patient comparisons, the error variance (noise) of the experiment can be reduced, thereby. Unfortunately, comparisons made on this basis have potential disadvantages. Treatments may have effects on experimental units other than those to which they were assigned (carry-across effects). Such effects cannot be estimated from split-mouth data. Neither can treatment effects be estimated. The estimable parameter in a split-mouth design is the treatment effect plus the sum of all carry-across effects. Unless a priori knowledge indicates that no carry-across effects exist, reported estimates of treatment efficacy are potentially biased. In the design of split-mouth clinical trials, potential gain in precision should be carefully weighed against a potential decrease in validity.[58] Regarding sample size, only 2 out of 38 trials of the current systematic review, included large subjects samples and only one of them surpassed the 100 participants.[22,25] Nevertheless, differences were observed also among control groups, as only 14 trials used placebo gel or distilled water (as placebo mouthwash). It is obvious that the trials having used placebo regimens showed a better form of blinding during their research.

Confounding factors include a variety of risk factors that can intermediate the result of periodontal treatment modalities. Main representers of this category are smoking, obesity, drug-induced gingival overgrowth, stress, metabolic syndrome, and other systematic diseases such as diabetes mellitus and atherosclerotic cardiovascular diseases.[59] The analysis of the trials included in the systematic review revealed no information regarding the aforementioned factors besides the free medical history of patients and controls in some of the trials. Future trial planning should consider confounding factors to accomplish safe and successful conclusions.

Risk of bias analysis revealed that merely 2 out of 8 studies in gingivitis therapy group, 1 out of 20 studies in nonsurgical group, and 6 out of 10 studies in surgical group, but with great heterogeneity in surgical procedures, were evaluated as having an overall low risk of bias, which was a prohibitive finding for proceeding to meta-analysis. In addition, a meta-analysis could not be performed, due to the great heterogeneity of the chemical characteristics and concentrations of the products applied.

Conclusion

Due to the large heterogeneity of the studies included and the insufficient number of randomized controlled trials with a low risk of bias, no meta-analysis was able to be conducted. Albeit the adjunct use of HA leads in improved clinical course when combined to either gingivitis therapy, nonsurgical, or surgical periodontal treatment. The topical use of HA seems to be safe as no adverse effects were detected at any of the studies. More trials are needed to be conducted with appropriate design in order to specify the ideal regimen of HA-based treatment modalities.

Supplementary Material

A Supplemental Appendix to this article is available online on the website of www.thejcdp.com.

Authors' Contributions

KP and DS contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. KS contributed to conception, design, and critically revised the manuscript.

References

1. Flemming HC, Wingender J. The biofilm matrix. Nat Rev Microbiol 2010;8(9):623–633. DOI: 10.1038/nrmicro2415.
2. Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. J Periodontol 1965;36:177–187. DOI: 10.1902/jop.1965.36.3.177.
3. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4(1):1–6. DOI: 0.1902/annals.1999.4.1.1.
4. Albandar JM. A 6-year study on the pattern of periodontal disease progression. J Clin Periodontol 1990;17(7 Pt 1):467–471. DOI: 10.1111/j.1600-051x.1990.tb02346.x.
5. Lindhe J, Socransky SS, Nyman S, et al. "Critical probing depths" in periodontal therapy. J Clin Periodontol 1982;9(4):323–336. DOI: 10.1111/j.1600-051x.1982.tb02099.x.
6. Badersten A, Nilveus R, Egelberg J. Effect of nonsurgical periodontal therapy. II. Severely advanced periodontitis. J Clin Periodontol 1984;11(1):63–76. DOI: 10.1111/j.1600-051x.1984.tb01309.x.
7. Ramfjord SP, Knowles JW, Nissle RR, et al. Results following three modalities of periodontal therapy. J Periodontol 1975;46(9):522–526. DOI: 10.1902/jop.1975.46.9.522.
8. Necas J, Bartosikova L, Brauner P, et al. Hyaluronic acid (hyaluronan): a review. Vet Med 2008;53(8):397–411. DOI: 10.17221/1930-VETMED.
9. Bukhari SNA, Roswandi NL, Waqas M, et al. Hyaluronic acid, a promising skin rejuvenating biomedicine: a review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. Int J Biol Macromol 2018;120(Pt B):1682–1695. DOI: 10.1016/j.ijbiomac.2018.09.188.

10. Håkansson L, Hällgren R, Venge P. Regulation of granulocyte function by hyaluronic acid. *In vitro* and *in vivo* effects on phagocytosis, locomotion, and metabolism. J Clin Invest 1980;66(2):298–305. DOI: 10.1172/JCI109857.
11. Dahiya P, Kamal R. Hyaluronic acid: a boon in periodontal therapy. N Am J Med Sci 2013;5(5):309–315. DOI: 10.4103/1947-2714.112473.
12. Bertl K, Bruckmann C, Isberg PE, et al. Hyaluronan in non-surgical and surgical periodontal therapy: a systematic review. J Clin Periodontol 2015;42(3):236–246. DOI: 10.1111/jcpe.12371.
13. Casale M, Moffa A, Vella P, et al. Hyaluronic acid: perspectives in dentistry. A systematic review. Int J Immunopathol Pharmacol 2016;29(4):572–582. DOI: 10.1177/0394632016652906.
14. Eliezer M, Imber J-C, Sculean A, et al. Hyaluronic acid as adjunctive to non-surgical and surgical periodontal therapy: a systematic review and meta-analysis. Clin Oral Investig 2019;23(9):3423–3435. DOI: 10.1007/s00784-019-03012-w.
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097. DOI: 10.1371/journal.pmed.1000097.
16. Higgins JP, Savović J, Page MJ, et al. Chapter 8: assessing risk of bias in a randomized trial 2021. Online information available at: www.training.cochrane.org/handbook.
17. Cardoso L, Silva R, de Almeida GGF, et al. A bibliometric model to analyze country research performance: scival topic prominence approach in tourism, leisure and hospitality. Sustainability (Switzerland) 2020; 12:1–27. DOI: 10.3390/su12239897.
18. Jentsch H, Pomowski R, Kundt G, et al. Treatment of gingivitis with hyaluronan. J Clin Periodontol 2003;30(2):159–164. DOI: 10.1034/j.1600-051x.2003.300203.x.
19. Pistorius A, Martin M, Willershausen B, et al. The clinical application of hyaluronic acid in gingivitis therapy. Quintessence Int 2005;36(7–8):531–538. PMID: 15999421.
20. Rodrigues SV, Acharya AB, Bhadbhade S, et al. Hyaluronan-containing mouthwash as an adjunctive plaque-control agent. Oral Health Prev Dent 2010;8(4):389–394. PMID: 21180677.
21. Sapna N, Vandana KL. Evaluation of hyaluronan gel (Gengigel(®)) as a topical applicant in the treatment of gingivitis. J Investig Clin Dent 2011; 2(3):162–170. DOI: 10.1111/j.2041-1626.2011.00064.x.
22. Sahayata VN, Bhavsar NV, Brahmbhatt NA. An evaluation of 0.2% hyaluronic acid gel (Gengigel ®) in the treatment of gingivitis: a clinical and microbiological study. Oral Health Dent Manag 2014;13(3):779–785. PMID: 25284557.
23. Gizligoz B, Ince Kuka G, Tunar OL, et al. Plaque inhibitory effect of hyaluronan-containing mouthwash in a 4-Day non-brushing model. Oral Health Prev Dent 2020;18(1):61–70. DOI: 10.3290/j.ohpd.a43936.
24. Al-Shabeeb AKH, Mohammed AN. Clinicalevaluation of 0.2% hyaluronic acid and its effect on the level of interleukine-1B in gingival crevicular fluid before and after treatment of plaque induced gingivitis. Ind J Public Health Res Develop 2019;10(2):659–664. DOI: 10.5958/0976-5506.2019.00368.1.
25. Abdulkareem AA, Al Marah ZA, Abdulbaqi HR, et al. A randomized double-blind clinical trial to evaluate the efficacy of chlorhexidine, antioxidant, and hyaluronic acid mouthwashes in the management of biofilm-induced gingivitis. Int J Dent Hyg 2020;18(3):268–277. DOI: 10.1111/idh.12432.
26. Engström PE, Shi XQ, Tronje G, et al. The effect of hyaluronan on bone and soft tissue and immune response in wound healing. J Periodontol 2001;72(9):1192–1200. DOI: 10.1902/jop.2000.72.9.1192.
27. Xu Y, Höfling K, Fimmers R, et al. Clinical and microbiological effects of topical subgingival application of hyaluronic acid gel adjunctive to scaling and root planing in the treatment of chronic periodontitis. J Periodontol 2004;75(8):1114–1118. DOI: 10.1902/jop.2004.75.8.1114.
28. Johannsen A, Tellefsen M, Wikesjö U, et al. Local delivery of hyaluronan as an adjunct to scaling and root planing in the treatment of chronic periodontitis. J Periodontol 2009;80(9):1493–1497. DOI: 10.1902/jop.2009.090128.
29. Pilloni A, Annibali S, Dominici F, et al. Evaluation of the efficacy of an hyaluronic acid-based biogel on periodontal clinical parameters. A randomized-controlled clinical pilot study. Ann Stomatol (Roma) 2011;2(3-4):3–9. PMCID: PMC3314319.
30. Koshal A, Bolt R, Galgut P. A comparison in postoperative healing of sites receiving non-surgical debridement augmented with and without a single application of hyaluronan 0.8% gel. DENTAL TRIBUNE Middle East & Africa Edition 2012. Online information Available at: http://www.takara-net.com.
31. Gontiya G, Galgali SR. Effect of hyaluronan on periodontitis: a clinical and histological study. J Indian Soc Periodontol 2012;16(2):184–192. DOI: 10.4103/0972-124X.99260.
32. Bevilacqua L, Eriani J, Serroni I, et al. Effectiveness of adjunctive subgingival administration of amino acids and sodium hyaluronate gel on clinical and immunological parameters in the treatment of chronic periodontitis. Ann Stomatol (Roma) 2012;3(2):75–81. PMCID: PMC3476496.
33. Chauhan AS, Bains VK, Gupta V, et al. Comparative analysis of hyaluronan gel and xanthan-based chlorhexidine gel, as adjunct to scaling and root planing with scaling and root planing alone in the treatment of chronic periodontitis: a preliminary study. Contemp Clin Dent 2013;4(1):54–61. DOI: 10.4103/0976-237X.111619.
34. Eick S, Renatus A, Heinicke M, et al. Hyaluronic acid as an adjunct after scaling and root planing: a prospective randomized clinical trial. J Periodontol 2013;84(7):941–949. DOI: 10.1902/jop.2012.120269.
35. Rajan P, Baramappa R, Rao NM, et al. Hyaluronic acid as an adjunct to scaling and root planing in chronic periodontitis. A randomized clinical trail. J Clin Diagn Res 2014;8(12):11–14. DOI: 10.7860/JCDR/2014/8848.5237.
36. Polepalle T, Srinivas M, Swamy N, et al. Local delivery of hyaluronan 0.8% as an adjunct to scaling and root planing in the treatment of chronic periodontitis: a clinical and microbiological study. J Indian Soc Periodontol 2015;19(1):37–42. DOI: 10.4103/0972-124X.145807.
37. Sharma V, Gupta R, Dahiya P, et al. Comparative evaluation of coenzyme Q_{10}-based gel and 0.8% hyaluronic acid gel in treatment of chronic periodontitis. J Indian Soc Periodontol 2016;20(4):374–380. DOI: 10.4103/0972-124X.183097.
38. Shah SA, Vijayakar HN, Rodrigues SV, et al. To compare the effect of the local delivery of hyaluronan as an adjunct to scaling and root planing versus scaling and root planing alone in the treatment of chronic periodontitis. J Indian Soc Periodontol 2016;20(5):549–556. DOI: 10.4103/0972-124X.201695.
39. Mallikarjun S, Neelakanti A, Babu HM, et al. Neutrophil elastase levels in the gingival crevicular fluid following hyaluronan gel application in the treatment of chronic periodontitis: a randomized split-mouth study. Indian J Dent Res 2016;27(4):397–404. DOI: 10.4103/0970-9290.191889.
40. Omer, B, Satti A, Gismalla, B, et al. The effect of local application of hyaluronan gel as an adjunctive to scaling and root planing in chronic periodontitis patients. African J Dent 2018;6(5):163–170. ISSN: 3216-0216.
41. Al-Shammari NM, Shafshak SM, Ali MS. Effect of 0.8% hyaluronic acid in conventional treatment of moderate to severe chronic periodontitis. J Contemp Dent Pract 2018;19(5):527–534. PMID: 29807962.
42. Lobato JCRF, Dos Santos Vilhena MA, Izidoro C, et al. Single application of 0.8% hyaluronic acid as a coadjuvant of nonsurgical treatment in nonsmoking patients with periodontitis: A split-mouth, randomized, controlled pilot clinical trial. J Indian Soc Periodontol 2019; 23(6):545–548. DOI: 0.4103/jisp.jisp_674_18.
43. Mahmood AA, Abdul-Wahab GA, Al-Karawi SI. Effect of hyaluronan and metronidazole gels in management of chronic periodontitis. J Int Oral Health 2019;11(3):158–163. DOI: 10.4103/jioh.jioh_292_18.
44. Ibraheem LM, Abdulhameed BS, Wifaq MA, et al. The effect of Hyaluronic Acid as an Adjunct after Scaling and Root Planning in the Treatment of Chronic Periodontitis. Indian J Public Health Res Develop. 2020;11:357–363. DOI: 10.37506/ijphrd.v11i10.11174.
45. Aydinyurt HS, Akbal D, Altindal D, et al. Evaluation of biochemical and clinical effects of hyaluronic acid on non-surgical periodontal

treatment: a randomized controlled trial. Ir J Med Sci 2020;189(4):1485–1494. DOI: 10.1007/s11845-020-02230-6.
46. Galli F, Zuffetti F, Capelli M, et al. Hyaluronic acid to improve healing of surgical incisions in the oral cavity: a pilot multicentre placebo-controlled randomised clinical trial. Eur J Oral Implantol 2008;1(3):199–206. PMID: 20467622.
47. Fawzy El-Sayed KM, Dahaba MA, Aboul-Ela S, et al. Local application of hyaluronan gel in conjunction with periodontal surgery: a randomized controlled trial. Clin Oral Investig 2012;16(4):1229–1236. DOI: 10.1007/s00784-011-0630-z.
48. Briguglio F, Briguglio E, Briguglio R, et al. Treatment of infrabony periodontal defects using a resorbable biopolymer of hyaluronic acid: a randomized clinical trial. Quintessence Int 2013;44(3):231–240. DOI: 10.3290/j.qi.a29054. PMID: 23444204.
49. Kumar R, Srinivas M, Pai J, et al. Efficacy of hyaluronic acid (hyaluronan) in root coverage procedures as an adjunct to coronally advanced flap in Millers Class I recession: a clinical study. J Indian Soc Periodontol 2014;18(6):746–750. DOI: 10.4103/0972-124X.147411.
50. Gupta S, Kediege SD, Gupta A, et al. Evaluation of Gengigel® application in the management of furcation with coronally advanced flap through surgical re-entry: a split mouth clinical study. J Clin Diagn Res 2017;11(1):ZC27–ZC32. DOI: 10.7860/JCDR/2017/21938.9169.
51. Pilloni A, Schmidlin PR, Sahrmann P, et al. Effectiveness of adjunctive hyaluronic acid application in coronally advanced flap in Miller class I single gingival recession sites: a randomized controlled clinical trial. Clin Oral Investig 2019;23(3):1133–1141. DOI: 10.1007/s00784-018-2537-4.
52. Reddy SP, Koduganti RR, Panthula VR, et al. Efficacy of low-level laser therapy, hyaluronic acid gel, and herbal gel as adjunctive tools in gingivectomy wound healing: a randomized comparative clinical and histological study. Cureus 2019;11(12):e6438. DOI: 10.7759/cureus.6438.
53. Marwa M, Mai SA, Eatmad AS. Clinical evaluation of hyaluronan gel alone or in combination with platelet-rich fibrin (PRF) in periodontal regenerative surgery. Al-Azhar Dent J Girls 2020;7:273–279. DOI: 10.21608/ADJG.2020.7697.1091.
54. Pilloni A, Rojas MA, Marini L, et al. Healing of intrabony defects following regenerative surgery by means of single-flap approach in conjunction with either hyaluronic acid or an enamel matrix derivative: a 24-month randomized controlled clinical trial. Clin Oral Investig 2021(8);25:5095–5107. DOI: 10.1007/s00784-021-03822-x.
55. Mamajiwala AS, Sethi KS, Raut CP, et al. Clinical and radiographic evaluation of 0.8% hyaluronic acid as an adjunct to open flap debridement in the treatment of periodontal intrabony defects: randomized controlled clinical trial. Clin Oral Investig 2021;25(9):5257–5271. DOI: 10.1007/s00784-021-03834-7.
56. Mühlemann HR, Son S. Gingival sulcus bleeding: a leading symptom in initial gingivitis. Helv Odontol Acta 1971;15(2):107–113. PMID: 5315729.
57. Miller PD. A classification of marginal tissue recession. Int J Periodontics Restorative Dent 1985;5(2):8–13. PMID: 3858267.
58. Hujoel PP, DeRouen TA. Validity issues in split-mouth trials. J Clin Periodontol 1992;19(9 Pt 1):625–627. DOI: 10.1111/j.1600-051x.1992.tb01709.x.
59. Hughes FJ, Bartold PM. Periodontal complications of prescription and recreational drugs. Periodontol 2000 2018;78(1):47–58. DOI: 10.1111/prd.12230.