Ref: Ro J Stomatol. 2022;68(4)
DOI: 10.37897/RJS.2022.4.6

A brief overview on the applications of hyaluronic acid in periodontal therapy

Andrada Soanca[1], Vlad Mastica[1], Emoke Pall[2], Alexandra Roman[1], Andreea Ciurea[1], Diana Onet[1], Iulia Cristina Micu[1], Darian Rusu[3]

[1]Department of Periodontology, Faculty of Dental Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Veterinary Reproduction, Obstetrics and Gynecology, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania
[3]Department of Periodontology, "Anton Sculean" Research Center of Periodontal and Peri-implant Diseases, Faculty of Dental Medicine, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

ABSTRACT

Hyaluronic acid (HA) is a component of the extracellular matrix of the non-mineralized and mineralized tissues, including the periodontium. HA have important physiological and biological properties. HA maintains the tissue volume, presents bacteriostatic, anti-inflammatory, osteoinductive, and angiogenetic properties, as well as stimulates many cell functions having a role in wound healing. HA has been used as an adjunctive in the treatment of gingivitis, periodontitis, gingival recessions, or in the reconstruction of papilla deficiencies. In periodontitis patients, the association of HA with subgingival mechanical instrumentation reduces local inflammation and its use with access flap results in larger attachment level gain of infrabony defects compared to control groups non treated with HA. HA application in conjunction with advanced flaps may improve gingival recession levels. HA injection for papillary deficiency seems to be a viable treatment option that improves clinical volume, esthetic outcomes and is associated with minimal pain.

Keywords: hyaluronic acid, periodontitis, periodontal therapy, regeneration

INTRODUCTION

Periodontitis is one of the most frequent infectious inflammatory diseases in humans, caused by bacteria from the subgingival dental plaque [1]. The periodontal destruction occurring in periodontitis leads to tooth mobility, secondary migrations and in the end to tooth loss, thus affecting the patient's functions, esthetics, and quality of life [2,3].

The main purpose of periodontal therapy is to stop the evolution of the periodontitis by acting on the dysbiotic biofilm, through some nonsurgical and surgical interventions depending on the severity of the disease. The keystone of periodontitis therapy is a non-surgical approach mostly based on the subgingival mechanical instrumentation [4], which changes the subgingival environment and improves the clinical parameters [3,5]. The subgingival mechanical instrumentation results in many periodontitis cases in important improvements even disease stabilization [6] but, in some cases, it fails to eradicate infection or inflammation [4]. Adjunctive, local antimicrobial treatments are recommended in some clinical circumstances to improve the efficacy of the subgingival instrumentation [6]. The use of locally administrated physical means such laser and photodynamic therapy is prohibited by the current practical treatment guide and there are no firm recommendations on the use of specific antimicrobial adjuvant products in periodontitis therapy [6]. Com-

Corresponding authors:
Iulia Cristina Micu, Alexandra Roman
E-mail: i.cristina.micu@gmail.com, veve_alexandra@yahoo.com

Article History:
Received: 5 December 2022
Accepted: 19 December 2022

plex surgical approaches are recommended to treat intrabony defects in severe periodontitis with the ultimate goal to regenerate the lost tissues [7], but despite the use of many techniques or biomaterials [1,8,9] the complete clinical success or periodontal regeneration are randomly obtained [1].

Miller class 1 and 2 gingival recessions (GR) is frequently encountered in clinical practice. GR are mostly of traumatic origin [10] and root coverage procedures aim to completely cover the exposed roots [10-12], although little is known on the quality of healing at the soft tissue-root surface interface. Some biomaterials including bioactive agents like enamel matrix derivatives (EMD), hyaluronic acid (HA) have been associated with surgical procedures in order to stimulate local regeneration [13].

The interdental papilla deficiencies as consequence of periodontitis evolution create esthetic and functional problems [14-16] and their surgical reconstruction [14] or nonsurgical management [14,17] still induces unpredictable results.

In these circumstances, new additional approaches, or products with a wide range of effects on periodontal healing processes that could ameliorate the reconstruction of the periodontal lost tissues of different origin are seeking [4,18]. HA emerged as promising a local product to be used adjunctively to surgical or nonsurgical periodontal therapies due to their pleiomorphic effects [19-21]. The studies reporting the use of HA to treat periodontal diseases provide inconsistent information [14]. Furthermore, the majority of these studies did not specify the exact type and molecular weight of the HA-based agents which explain the heterogeneity of the reported results and prevent to draw firm conclusions on its clinical efficacy [4].

The aim of this paper is to briefly discuss the characteristics of HA and present the different applications of HA products in periodontal treatments.

NATURE, PROPERTIES, AND USES OF HYALURONIC ACID

Polysaccharides are important compounds used in tissue engineering and they can be found from several natural sources such as plants, animals, fungi, insects [22,23]. HA is a natural polymer belonging to the glycosaminoglycan family and consists of two sugars, glucuronic acid and N-acetyl-glucosamine [22]. HA has a high molecular weight ranging between 1000 to 20,000,000 Da which influences its physiochemical and biological properties [1]. This molecule typically can be found in different body fluids like the synovial fluid, saliva, serum, gingival crevicular fluid [24]. HA is a component of the extracellular matrix of the non-mineralized and mineralized tissues, including the periodontium [25,26].

HA have important physiological and biological properties. HA is the most hygroscopic natural molecule, that helps maintaining the tissue volume lubrication and resilience [26, 27], and its viscoelasticity prevents viral and bacterial intratissular penetration [28]. Also, HA presents bacteriostatic, anti-inflammatory [29,30], antiedematous [27], osteoinductive [31-35], and angiogenetic properties, and stimulates cell migration, adhesion, and proliferation [36,37], which play an essential role in wound healing of mineralized and non-mineralized tissues [24,38]. Based on these properties, HA gained an important interest in medical applications [39,40]. HA application during surgical procedure could favor a normal healing of the tissue without scar formation [41].

HA AND PERIODONTAL THERAPY

HA in gingivitis treatment

Local applications of a 0.2% HA-based gel, twice daily for three weeks in association with correct oral hygiene, in patients with plaque-induced gingivitis, statistically significantly improved plaque and bleeding indices and decreased the peroxidase and lysozyme activities in the crevicular fluid, compared with placebo-treated patients [42].

In gingivitis patients, statistically significant reduction of gingival and papillary bleeding index was reported after applications of a HA-containing gel plus scaling as compared with placebo gel plus scaling or only scaling [43].

Local application of HA-based products seems to ameliorate local inflammation in plaque-induced gingivitis.

HA associated with nonsurgical periodontitis therapy

Some studies showed that the application of a HA gel associated to subgingival mechanical instrumentation in periodontitis patients improved the clinical parameters in terms of gingival index, bleeding index, reduction of local inflammatory signs and probing depths (PD) [44-47].

In a split mouth clinical study, subgingival application of 0,2 mL of 0,8% HA gel following subgingival mechanical instrumentation significantly reduced gingival bleeding index, PD, and clinical attachment level as compared with subgingival mechanical instrumentation alone [48].

A randomized clinical trial including chronic periodontitis patients showed that two weeks applications of two molecular weights hyaluronan gels as adjunctive of subgingival mechanical instrumentation had significant improvements on PD and periodontopathogens count reductions as compared with subgingival mechanical instrumentation alone [47]. This suggests that HA may prevent recolonization of pathogens in subgingival areas [47].

The evaluation of gingival crevicular fluid [45] or tissue biopsies [44,49] in patients with periodontitis,

showed that the sites treated with HA gels in association with the mechanical subgingival instrumentation displayed a tendency for reduced levels of inflammation when compared to control sites [46,50,51].

A randomized controlled clinical trial on moderate periodontitis patients showed that hyaluronic acid gel adjunctive to subgingival mechanical instrumentation statistically significantly improved gingival bleeding index, PD and clinical attachment level as compared with subgingival mechanical instrumentation alone, after three months [4]. Clinical attachment gain may indicate periodontal reparation or regeneration after HA-gel applications [4].

The benefits of using HA based products as adjunctive therapy to subgingival instrumentation seem to manifest through a reduction in bleeding on probing and a gain in CAL, both indicating the inflammation resolution and periodontal regeneration.

HA associated with periodontal pocket reduction surgery

The periodontal pocket surgical therapy treats the non-responding sites to the nonsurgical treatment, which are residual pockets ≥6 mm [6] and includes access flap approaches, resective periodontal surgery, or regenerative periodontal surgery [6].

In the treatment of infrabony defects in periodontitis patients, the use of hyaluronic acid induced some clinical benefits over access flap [52]. Long-term randomized clinical trials showed that access flap debridement associated with application of HA products improved clinical parameters in terms of attachment level gain and PD reduction [53, 54] and induced radiographic benefits [54] as compared with access flap alone.

A randomized clinical trial reported that, as compared with access flap surgery, HA plus access flap significantly ameliorate clinical parameters such as PD and attachment level [55].

Other studies with shorter follow up periods or without control groups evaluated the impact of HA in the surgical management of periodontal infrabony defects. A split-mouth clinical study reported that as compared to modified Widman flap procedure, treated sites with 0,8% HA gel associated with modified Widman flap surgery displayed statistically significant improvements of clinical attachment level and GR dimension, after 3 and 6 month-follow-up [40].

In infrabony pockets, HA plus membrane placement surgery induced an increase of bone height on radiographs (mean value 2.2%) as compared with sites treated only with membrane. Moreover, scaling alone or scaling plus HA applications in pockets associated with infrabony defects both induced a decrease of bone height, without differences between these two nonsurgical approaches [56].

A radiographic bone remodeling and the filling of the intrabony defects in association with a clinical attachment gain of 2.6 mm were reported after a surgical approach consisting in application of autologous bone plus an esterified low-molecular HA product, suggesting that HA might accelerate new bone formation in the infrabony defects [57].

HA packed fibers applied intrasurgically in deep periodontal defects reduced PD mean by 5.8 mm, as well as increased GR by 2.0 mm and attachment level by 3.8 mm, after one year [58].

Most of studies described a positive statistically significant effects of HA application, alone or with flap surgery, or other biomaterials, in terms of clinical periodontal outcome variables. No adverse effects were associated with HA application in these clinical situations.

HA in the treatment of gingival recession

A recent systematic review and meta-analysis reported that HA could improve the results of coronally advanced flap procedures through its role in wound healing process and regeneration of periodontal tissue [13].

The addition of HA to coronally advanced flap to cover GR significantly reduced GR dimensions and increased clinical attachment level as well as complete root coverage rate compared to the use of CAF alone [59].

Statistically significant benefits in terms of mean reduction of GR after HA application plus coronally advanced flap were reported as compared to the surgery alone, but no significant differences were observed in terms of GR reduction [60,61].

Modified coronally advanced tunnel technique combined with subepithelial connective tissue graft plus HA treating multiple GR seemed not to improve the results of the bilayer surgical procedure alone, at 6 months follow-up. However, HA seemed to improve the soft tissue quality [62].

HA in papilla reconstruction

Becker et al. (2010) presented for the first time the idea of injecting HA in the deficient papilla [63]. A recent review reported the effects of HA injection for interdental papillae reconstruction, but no comparison or analyze was possible due to the great heterogeneity of the protocols and materials employed. However, all studies showed statistically significant improvements in most of the cases with a volume filling ranging between 19%-100% [17]. A more recent systematic review performed the meta-analysis of the data from 18 studies reporting a proportion of 47% (confidence interval [CI]:35–59%) of sites with complete interdental papilla reconstruction [14].

Non-surgical HA injections seem to be effective in reconstructing papillary volume [63], improving

significantly clinical [15,64] and patient-centered outcomes [15,64].

Although all studies reported an efficient papillary volume restoration after HA use, further controlled RTC with standardized parameters and long-term follow-up are recommended.

CONCLUSIONS

The association of HA with subgingival mechanical instrumentation reduces local inflammation in periodontitis patients.

The evidence suggests that HA could play a potential role in periodontal tissue healing. Thus, adjunctive use of HA to regenerative pocket reduction surgical approaches may result in greater attachment level gain compared to non- HA-treated control sites. HA application in conjunction with advanced flaps may improve gingival recession levels.

HA injection for papillary deficiency seems to be a viable treatment option that improves clinical volume, esthetic outcomes and is associated with minimal pain.

The use of HA associated to periodontal treatments is generally safe, without any adverse effects.

Acknowledgement

This work was carried out within Doctoral Research Project supported by University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania, Contract No.: 881/30/12.01.22.

Conflict of interest: none declared
Financial support: none declared

Acknowledgments: all authors contributed equally to the manuscript.

REFERENCES

1. Rodríguez-Aranda M, Iborra-Badia I, Alpiste-Illueca F, López-Roldán A. Hyaluronic acid for periodontal tissue regeneration in intrabony defects. A systematic review. *Dentistry Review.* 2022;2(3):100057. doi: 10.1016/j.dentre.2022.100057
2. Abedi N, Rajabi N, Kharaziha M, Nejatidanesh F, Tayebi L. Layered scaffolds in periodontal regeneration. *J Oral Biol Craniofac Res*. 2022 Nov-Dec;12(6):782-97. doi: 10.1016/j.jobcr.2022.09.001
3. Micu IC, Muntean A, Roman A, Stratul SI, Pall E, Ciurea A et al. A Local Desiccant Antimicrobial Agent as an Alternative to Adjunctive Antibiotics in the Treatment of Periodontitis: A Narrative Review. *Antibiotics* 2023;12:456. doi: 10.3390/antibiotics12030456
4. Olszewska-Czyz I, Kralik K, Prpic J. Biomolecules in Dental Applications: Randomized, Controlled Clinical Trial Evaluating the Influence of Hyaluronic Acid Adjunctive Therapy on Clinical Parameters of Moderate Periodontitis. *Biomolecules* 2021;11:1491. doi: 10.3390/biom11101491
5. Suvan J, Leira Y, Moreno Sancho FM, Graziani F, Derks J, Tomasi C. Subgingival instrumentation for treatment of periodontitis. A systematic review. *J Clin Periodontol*. 2020;47:155–75. doi: 10.1111/jcpe.13245
6. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Beglundh T et al. EFP Workshop Participants and Methodological Consultants. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol*. 2020;47:4–60. doi: 10.1111/jcpe.13290
7. Somerman MJ, Ouyang HJ, Berry JE, Saygin NE, Strayhorn CL, D' Errico et al. Evolution of periodontal regeneration: from the roots' point of view. *J Periodontal Res.* 1999;34:420. doi: 10.1111/j.1600-0765.1999.tb02276.x
8. Hammarström L. Enamel matrix, cementum development and regeneration. *J Clin Periodontol.* 1997;24:658–68. doi: 10.1111/j.1600-051x.1997.tb00247.x
9. Sculean A, Windisch P, Szendröi-Kiss D, Horváth A, Rosta P, Becker J et al. Clinical and histologic evaluation of an enamel matrix derivative combined with a biphasic calcium phosphate for the treatment of human intrabony periodontal defects. *J Periodontol*. 2008; 79(10):1991-9. doi: 10.1902/jop.2008.080009
10. Zucchelli G, Mounssif I. Periodontal plastic surgery. *Periodontol 2000.* 2015;68(1):333–68. doi: 10.1111/prd.12059
11. De Sanctis M, Zucchelli G. Coronally advanced flap: a modified surgical approach for isolated recession-type defects: three-year results. *J Clin Periodontol*. 2007;34(3):262–8. doi: 10.1111/j.1600-051X.2006.01039.x
12. Chambrone L, Tatakis DN. Periodontal soft tissue root coverage procedures: A systematic review from the AAP Regeneration Workshop. *J Periodontol*. 2015;86(Suppl.S2) S8–S51. doi: 10.1902/jop.2015.130674
13. Rojas MA, Marini L, Sahrmann P, Pilloni A. Hyaluronic Acid as an Adjunct to Coronally Advanced Flap Procedures for Gingival Recessions: A Systematic Review and Meta – Analysis of Randomized Clinical Trials. *J Pers Med* 2022;12:1539. doi: 10.3390/jpm12091539
14. Fae DS, de Aquino SN, Correa FOB, Correa Rabelo C, Pontes AEF, Araujo Lemos CA. Hyaluronic acid gel as a nonsurgical approach for the interdental papillary defects: A systematic review, *Dentistry Review*. 2023;3:100066. doi: 10.1016/j.dentre.2023.100066
15. Lee WP, Kim HJ, Yu SJ, Kim BO. Six Month Clinical Evaluation of Interdental Papilla Reconstruction with Injectable Hyaluronic Acid Gel Using an Image Analysis System. *J Esthet Restor Dent*. 2016;28221-30. doi: 10.1111/jerd.12216
16. Carnio J, Carnio AT. Papilla reconstruction: Interdisciplinary consideration for clinical success. *J Esthet Restor Dent*. 2018;30:484-91. doi: 10.1111/jerd.12411
17. Lieppe T, Alliot C, Verner C, Badran Z, Soueidan A, Struillou X. Papillary Reconstruction using Hyaluronic Acid: A Review. *Oral Health Prev Dent*. 2022;20(1):421-31. doi: 10.3290/j.ohpd.b3556037
18. Zhai P, Peng X, Li B, Liu Y, Sun H, Li X. The application of hyaluronic acid in bone regeneration, *Int J Biol Macromol* 2020;151:1224-39. doi: 10.1016/j.ijbiomac.2019.10.169
19. Tomasi C, Koutouzis T, Wennström JL. Locally delivered doxycycline as an adjunct to mechanical debridement at retreatment of periodontal pockets. *J Periodontol*. 2008;79(3):431-9. doi: 10.1902/jop.2008.070383
20. Pilloni A, Zeza B, B, Kuis D et al. Treatment of residual periodontal pockets using a hyaluronic acid-based gel: a 12 month multicenter randomized triple-blinded clinical trial. *Antibiotics (Basel).* 2021;10(8):924. doi: 10.3390/antibiotics10080924
21. Pilloni A, Rojas MA, Trezza C, Carere M, De Filippis A, Marsala RL, Marini L. Clinical effects of the adjunctive use of polynucleotide and hyaluronic acid-based gel in the subgingival re-instrumentation of residual periodontal pockets: A randomized, split-mouth clinical trial. *J Periodontol*. 2022. doi: 10.1002/JPER.22-0225. Epub ahead of print. doi: 10.1002/JPER.22-0225. Epub ahead of print.
22. Saravanakumar K. Application of hyaluronic acid in tissue engineering, regenerative medicine, and nanomedicine: A review. *Int J Biol Macromol*. 2022;222:2744–60. doi: 10.1016/j.ijbiomac.2022.10.055
23. Ullah S, Khalil AA, Shaukat F, Song Y. Sources, extraction and biomedical properties of polysaccharides. *Foods.* 2019;8(8):304. doi: 10.3390/foods8080304
24. Bertl K, Bruckmann C, Isberg P-E, Klinge B, Gotfredsen K, Stavropoulos A. Hyaluronan in non-surgical and surgical periodontal therapy: a systematic review. *J Clin Periodontol*. 2015;42:236–46. doi: 10.1111/jcpe.12371
25. Pogrel MA, Lowe MA, Stern R. Hyaluronan (hyaluronic acid) in human saliva. *Arch Oral Biol*. 1996;41(7):667-71. doi: 10.1016/s0003-9969(96)00050-7

26. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med*. 1997;242(1):27-33. doi: 10.1046/j.1365-2796.1997.00170.x
27. Dahiya P, Kamal R. Hyaluronic Acid: a boon in periodontal therapy. *N Am J Med Sci*. 2013;5(5):309-15. doi: 10.4103/1947-2714.112473
28. Sutherland IW. Novel and established applications of microbial polysaccharides. *Trends Biotechnol*. 1998;16(1):41-6. doi: 10.1016/S0167-7799(97)01139-6
29. Laurent TC, Laurent UB, Fraser JR. Functions of hyaluronan. *Ann Rheum Dis*. 1995;54(5):429-32. doi: 10.1136/ard.54.5.429
30. Pirnazar P, Wolinsky L, Nachnani S, Haake S, Pilloni A, Bernard GW. Bacteriostatic effects of hyaluronic acid. *J Periodontol*. 1999;70(4):370-4. doi: 10.1902/jop.1999.70.4.370
31. Sasaki T, Watanabe C. Stimulation of osteoinduction in bone wound healing by high-molecular hyaluronic acid. *Bone*. 1995;16(1):9-15. doi: 10.1016/s8756-3282(94)00001-8
32. Mendes RM, Silva GA, Lima MF, Calliari MV, Almeida AP, Alves JB, Ferreira AJ. Sodium hyaluronate accelerates the healing process in tooth sockets of rats. *Arch Oral Biol*. 2008;53(12):1155-62. doi: 10.1016/j.archoralbio.2008.07.001
33. Mendes RM, Silva GA, Caliari MV, Silva EE, Ladeira LO, Ferreira AJ. Effects of single wall carbon nanotubes and its functionalization with sodium hyaluronate on bone repair. *Life Sci*. 2010;87(7-8):215-22. doi: 10.1016/j.lfs.2010.06.010
34. Kawano M, Ariyoshi W, Iwanaga K, Okinaga T, Habu M, Yoshioka I et al. Mechanism involved in enhancement of osteoblast differentiation by hyaluronic acid. *Biochem Biophys Res Commun.* 2011;405(4):575-80. doi: 10.1016/j.bbrc.2011.01.071
35. De Brito Bezerra B, Mendes Brazão MA, de Campos ML, Casati MZ, Sallum EA, Sallum AW. Association of hyaluronic acid with a collagen scaffold may improve bone healing in critical-size bone defects. *Clin Oral Implants Res*. 2012;23(8):938-42. doi: 10.1111/j.1600-0501.2011.02234.x
36. Burd DA, Greco RM, Regauer S, Longaker MT, Siebert JW, Garg HG. Hyaluronan and wound healing: a new perspective. *Br J Plast Surg.* 1991;44(8):579-84. doi: 10.1016/0007-1226(91)90093-y
37. Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. *Annu Rev Cell Dev Biol*. 2007;23:435-61. doi: 10.1146/annurev.cellbio.23.090506.123337
38. Casale M, Moffa A, Vella P, Sabatino L, Capuano F, Salvinelli B et al. Hyaluronic acid: Perspectives in dentistry. A systematic review. *Int J Immunopathol Pharmacol*. 2016;29(4):572-82. doi: 10.1177/0394632016652906
39. Robert L. Hyaluronan, a truly "youthful" polysaccharide. Its medical applications. *Pathol Biol (Paris).* 2015;63(1):32-4. doi: 10.1016/j.patbio.2014.05.019
40. Fawzy El-Sayed KM, Dahaba MA, Aboul-Ela S, Darhous MS. Local application of hyaluronan gel in conjunction with periodontal surgery: a randomized controlled trial. *Clin Oral Investig* 2012;16:1229–36. doi: 10.1007/s00784-011-0630-z
41. Sukumar S, Dřízhal I. Hyaluronic acid and periodontitis, *Acta Medica (Hradec Králové)* 2007;50(4):225–8. doi: 10.14712/18059694.2017.88
42. Jentsch H, Pomowski R, Kundt G, Göcke R. Treatment of gingivitis with hyaluronan. *J Clin Periodontol*. 2003;30(2):159-64. doi: 10.1034/j.1600-051x.2003.300203.x
43. Sahayata VN, Bhavsar NV, Brahmbhatt NA. An evaluation of 0.2% hyaluronic acid gel (Gengigel ®) in the treatment of gingivitis: a clinical & microbiological study. *Oral Health Dent Manag*. 2014;13(3):779-85. PMID: 25284557
44. Gontiya G, Galgali SR. Effect of hyaluronan on periodontitis: A clinical and histological study. *J Indian Soc Periodontol*. 2012;16(2):184-92. doi: 10.4103/0972-124X.99260
45. Xu Y, Höfling K, Fimmers R, Frentzen M, Jervøe-Storm PM. 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):1114-8. doi: 10.1902/jop.2004.75.8.1114
46. Johannsen A, Tellefsen M, Wikesjö U, Johannsen G. Local delivery of hyaluronan as an adjunct to scaling and root planing in the treatment of chronic periodontitis. *J Periodontol*. 2009;80(9):1493-7. doi: 10.1902/jop.2009.090128
47. Eick S, Renatus A, Heinicke M, Pfister W, Stratul SI, Jentsch H. Hyaluronic Acid as an adjunct after scaling and root planing: a prospective randomized clinical trial. *J Periodontol.* 2013;84(7):941-9. doi: 10.1902/jop.2012.120269
48. Polepalle T, Srinivas M, Swamy N, Aluru S, Chakrapani S, Chowdary BA. 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
49. Mesa FL, Aneiros J, Cabrera A. Antiproliferative effect of topical hyaluronic acid gel: Study in gingival biopsies of patients with periodontal disease. *Histol Histopathol*. 2002;17:747–53. doi: 10.14670/HH-17.747
50. Pilloni A, Annibali S, Dominici F, Di Paolo C, Papa M, Cassini MA, Polimeni A. 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
51. Bevilacqua L, Eriani J, Serroni I, Liani G, Borelli V, Castronovo G, Di Lenarda R. 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
52. Onisor F, Bran S, Mester A, Voina-Tonea A. Efficiency of Hyaluronic Acid in Infrabony Defects: A Systematic Review of Human Clinical Trials. Medicina (Kaunas). 2022;58(5):580. doi: 10.3390/medicina58050580
53. De Santana RB, de Santana CM. Human intrabony defect regeneration with rhFGF-2 and hyaluronic acid - a randomized controlled clinical trial. *J Clin Periodontol.* 2015;42(7):658-65. doi: 10.1111/jcpe.12406
54. Mamajiwala AS, Sethi KS, Raut CP, Karde PA, Mamajiwala BS. 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
55. Briguglio F, Briguglio E, Briguglio R, Cafiero C, Isola G. Treatment of infrabony periodontal defects using a resorbable biopolymer of hyaluronic acid: a randomized clinical trial. *Quintessence Int*. 2013;44(3):231-40. doi: 10.3290/j.qi.a29054
56. Engström PE, Shi XQ, Tronje G, Larsson A, Welander U, Frithiof L et al. The effect of hyaluronan on bone and soft tissue and immune response in wound healing. *J Periodontol* 2001;72:1192-200. doi: 10.1902/jop.2000.72.9.1192
57. Ballini A, Cantore S, Capodiferro S, Grassi FR. Esterified hyaluronic acid and autologous bone in the surgical correction of the infra-bone defects. *Int J Med Sci*. 2009;6(2):65-71. doi: 10.7150/ijms.6.65
58. Vanden Bogaerde L. Treatment of infrabony periodontal defects with esterified hyaluronic acid: clinical report of 19 consecutive lesions. *Int J Periodontics Restorative Dent.* 2009;29(3):315-23. PMID: 19537471
59. Pilloni A, Schmidlin PR, Sahrmann P, Sculean A, Rojas MA. 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):1133-41. Erratum in: *Clin Oral Investig*. 2018;22(8):2961-62. doi: 10.1007/s00784-018-2537-4
60. Rajan P, Rao NM, Nera M, Rahaman SM. Hyaluronon as an adjunct to coronally advanced flap for the treatment of gingival recession defects. *Natl J Integr Res Med*. 2015;6:94–100. Available: http://nicpd.ac.in/ojs-/index.php/njirm/article/view/891/773
61. Kumar R, Srinivas M, Pai J, Suragimath G, Prasad K, Polepalle T. 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;18:746–50. doi: 10.4103/0972-124X.147411
62. Górski B, Skierska I, Szerszeń M, Mańka-Malara K. Tunnel technique with cross-linked hyaluronic acid in addition to subepithelial connective tissue graft, compared with connective tissue graft alone, for the treatment of multiple gingival recessions: 6-month outcomes of a randomized clinical trial. *Clin Oral Investig*. 2023 Feb 3. doi: 10.1007/s00784-023-04887-6. Epub ahead of print.
63. Becker W, Gabitov I, Stepanov M, Kois J, Smidt A, Becker BE. Minimally invasive treatment for papillae deficiencies in the esthetic zone: a pilot study. *Clin Implant Dent Relat Res*. 2010;12(1):1-8. doi: 10.1111/j.1708-8208.2009.00247.x
64. Awartani FA, Tatakis DN. Interdental papilla loss: treatment by hyaluronic acid gel injection: a case series. *Clin Oral Investig*. 2016;20(7):1775-80. doi: 10.1007/s00784-015-1677-z