Review Article

DOI: 10.7860/JCDR/2023/59632.17485

Hyaluronic Acid in Periodontal Regeneration and Implant Dentistry- A Review

Dentistry Section

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ABSTRACT

The glycosaminoglycan Hyaluronic Acid (HA) is present in the connective tissue of vertebrates. In the extracellular matrix of soft periodontal tissues, it is the most prevalent glycosaminoglycan with a higher molecular weight. In medical fields such as orthopaedics, dermatology, and ophthalmology, the use of HA in the treatment of inflammatory processes is well established. The extracellular matrix of various tissues, including connective tissue, synovial fluid, and other tissues, contains HA, a naturally occurring linear polysaccharide. Its efficacy in the treatment of inflammatory conditions has been proven. It has anti-inflammatory and antibacterial effects in the treatment of gingivitis and periodontitis in dentistry. It could be used as an adjunct to mechanical therapy in the treatment of periodontitis because of its tissue healing properties. Use of HA for implant surface modification has also been extensively studied. HA has proven to be effective in peri-implantitis. The purpose of this review paper is to explain HA's involvement in periodontal therapy.

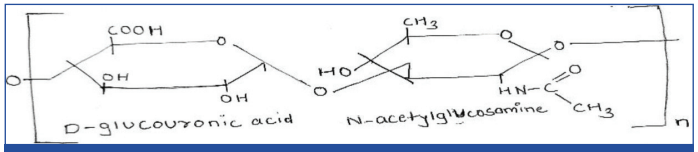
Keywords: Anti-inflammatory, Connective tissue, Hyaluronate, Peri-implantitis, Periodontal wound healing

INTRODUCTION

Hyaluronate also identified as hyaluronan or "HA", is a non sulphated, higher molecular mass linear polysaccharide present in connective tissue, synovial fluid, the extracellular matrix and other tissues. It has a variety of biological and physical functions, including extracellular, cellular, growth factor interactions, osmotic pressure regulation, and lubrication of tissue [1]. All of these roles contribute to the tissue's structural and homeostatic integrity. On periodontal tissues invaded by submicrobial flora, HA have antioedematous and anti-inflammatory properties [1].

Structure

The HA is a non sulphated glycosaminoglycan having naturally occurring 4,000-20,000,000 daltons molecular weight. The HA structure is made up of alternating 1-3 and 1-4 bonds connecting "polyanionic disaccharide units of glucouronic acid and N-acetyl glucosamine" [Table/Fig-1] [2]. It is a straight chain of polysaccharide found in synovial fluid, connective tissue, embryonic mesenchyma, skin, vitreous humour and a variety of other body organs and tissues. HA can be synthesised by almost all cells in the body, and the process occurs in cell membrane [1].



[Table/Fig-1]: Diagram of HA molecule based on information given by Dahiya P and Kamal R [2].
Image hand drawn by authors

History

Vedamurthy M mentioned in the study that Scientists John Palmer discovered HA in 1934 at Columbia University in New York, from the glassy jelly from eyes of cows, they isolated a chemical substance [3]. The initials HA were chosen because they were derived from the Greek word "hyalos," which means "glass." Preliminary clinical trials have been carried out in the field of dentistry by Vangelisti R et al., [4].

Peri-implantitis is initiated primarily by bacteria similarly as periodontitis, and HA has been proven to have antioedematous, anti-inflammatory, and antibacterial properties. The balance between Reactive Oxygen Species (ROS) and antioxidants has been discovered to be the most important requirement for healthy periodontal tissue which is provided by HA.

REVIEW

Mechanism of Action

Most cells in the body can synthesise HA, which is a major polysaccharide component of connective tissue's extracellular matrix [5]. It helps with tissue hydrodynamics, cell migration, and proliferation, as well as improving the tissue's healing properties [6]. HA helps in chemotaxis, proliferation, and effective differentiation of mesenchymal cells speed up regeneration of bone [7].

Source, Body Reservoir and Uptake of Hyaluronic Acid (HA)

The quantity of HA in human skin is estimated to be 5 grams. HA can be found in majority of periodontal tissues like gingiva and Periodontal Ligament (PDL). Hyaluronan Synthase (HAS) enzymes (HAS1, HAS2, and HAS3) synthesise high molecular weight Hyaluronan (HY) in gingiva and PDL, cementoblasts in cementum, and osteoblasts in alveolar bone, as well as in smaller amounts in mineralised tissues like alveolar bone and cementum [8].

Properties of Hyaluronic Acid (HA)

The HA is hygroscopic in nature, viscoelastic, has a bacteriostatic effect and is biocompatible, non antigenic having anti-inflammatory, antioedematous and antioxidant properties [8].

USE OF HA IN PERIODONTAL REGENERATION

Topical application of HA in subgingival regions has been found to minimise microbial activity, aid in bone regeneration in deep periodontal bony defects, and is useful in directed bone regeneration, non surgical treatment of peri-implantitis pockets, peri-implant maintenance of immediately inserted implants, and gingival augmentation in mucogingival surgery. Other molecules used in directed bone regeneration techniques and tissue engineering study, such as bone morphogenic protein-2 and platelet derived growth factor-BB, can serve as scaffolds for HA as was shown in study by Park KH et al. [9].

Infrabony Defect

Bogaerde LV investigated the therapeutic effectiveness of esterified HA in the management of deep periodontal infrabony defects [10]. The research treated 19 defects, 18 infrabony, and one mandibular molar furcation in 16 patients with a probing depth of atleast 6 mm. Esterified HA in the form of fibres (Hyaloss matrix, Meta) were directly packed into the coagulum to fill the defect after the granulation tissue was removed. Hyaloss matrix turned into a gel when it came into contact with liquids and filled the bone defect. The mean Probing Pocket Depth (PPD) was 5.8 mm lower a year after treatment, gingival recession was 2.0 mm higher, and attachment gain was 3.8 mm. The authors concluded that using HA to treat intrabony defects appears to be a promising approach.

In their report, Sehdev B et al., looked at the efficacy of HA coupled with a bioresorbable membrane for the management of infrabony defects [11]. A total of 24 infrabony defects were randomly allocated to assess (HA in conjunction with bioresorbable membrane) and monitor (bioresorbable membrane alone) treatment groups in twenty systemically stable patients. A computerised Florida disc probe and radiograph were used to assess PPD, relative attachment level, and relative gingival margin level at baseline and six months follow-up. For the treatment of human infrabony defects, a regenerative approach using hyaloss in conjunction with GTR resulted in a substantial increase in Clinical Attachment Loss (CAL) gain, reductions in PPD and radiographic defect fill, as well as linear bone growth, related to the GTR alone.

Gingival Recession

Several studies as those of Kumar R et. al. and Rajan P et. al, have indicated that using HA to treat gingival recession defects is a promising process [12,13]. Furthermore, Rajan P et al., found that HA, like subepithelial connective tissue graft, increased the possibility of achieving root coverage in Miller's class I and II recession [13].

Kumar R et al., investigated the efficiency of HY gel as a root covering complement to Coronally Advanced Flap (CAF) [12]. The study included ten participants with Miller's Class I gingival recession on the canine and premolar areas. HY gel (gengigel 0.2 percent gel, which is 0.2 percent HY gel) with CAF was utilised in the experimental group, while CAF alone was used in the control group. At baseline, 1, 3, 6, 12, and 24 weeks, the RD was measured, and the Pocket Depth (PD) and CAL were reported at 12 and 24 weeks. At baseline, the average PPD in experimental sites was 1.8 mm, compared to 2.0 mm in control sites. The mean PD in experimental sites was 1.7 mm after 24 weeks, while it was 2.0 mm in control sites. Both groups demonstrated a significant benefit and stability in clinical attachment at the 24-week follow-up. On average, experimental sites had an Recession Depth (RD) of 3.2 mm, while control sites had an RD of 2.9 mm. The mean RD in experimental sites was 1.1 mm after 24 weeks, whereas it was 1.0 mm in control sites. The experimental and control groups had 68.33 percent 28 percent root coverage and 61.67 percent 30.22 percent root coverage, respectively. When used as an alternative to the CAF protocol, the author concluded that HY has an impact on the treatment outcome.

Pilloni A et al., assess the benefits of using adjunctive HA in the CAF technique for single Miller class I/Recession Type 1 (RT1) gingival recession therapy [14]. The test group received CAF and HA therapy, while the control group received CAF alone (control group). The test group's recession reduction {2.7 mm (1.0)} was statistically substantially higher than the control group's {1.9 mm (1.0); p=0.007} after 18 months. PPD levels were found to be significantly greater in both groups, although the difference was not statistically significant. There was no statistically significant difference between treatments in terms of keratinised tissue benefit. Root coverage was 80 percent in the test sites and 33.3 percent in the control sites. The test sites had mean root coverage of 93.8 13.0 percent, while the control sites had root coverage of 73.1 20.8 percent. Seven days after surgery, the test group showed less swelling and pain. Pain severity did not show a statistically significant difference. As a result, the use of HA as a supplement was effective in achieving complete root coverage for single "Miller class I/RT1 gingival recession sites".

Papilla Reconstruction

One of the most difficult tasks is the construction of interdental papilla, particularly in the aesthetic region. Interdental papilla loss may occur for a number of reasons, including periodontal surgery or trauma. Bertl K et al., performed a randomised controlled trial to see whether HY injections could help complement deficient interproximal papillae at implant-supported crowns in the anterior maxilla [15]. Injection of HY adjacent to maxillary anterior implant-supported crowns did not result in clinically significant volume augmentation of defective papillae, according to the authors.

According to Becker W et al., HA gel is a synthetic material that can be used without causing drug interactions and is a healthy material that reduces the interdental black triangle in the aesthetic region [16]. The Food and Drug Administration has also given it their approval. HA was claimed to be dermal filler by Vedamurthy who used it for soft tissue augmentation and saw significant results [17]. Tanwar J and Hungund SA used a non surgical approach to inject 0.2 percent HA into the lost interdental papilla [18]. After injecting a local anaesthetic, a small amount of HA gel (less than 0.2 mL) was injected 2-3 mm apical to the coronal tip of the papilla. The gel's tolerance was unquestionably fine, with no signs of intolerance. The treatment patient did not show any progress after the first follow-up, which was three weeks later, so another shot of 0.2 percent HA injection was given. Photographs were used to take measurements of the black triangle. Photographs were taken after three months, and a comparison was made using these data. This procedure resulted in a substantial increase in papillary volume as well as noticeable aesthetic changes.

Use of HA in Implantology and Adjunctive Procedures

Nobre AM et al., compared the health of the peri-implant system during the healing time of immediate function implants using HA or CHX gels [19]. In contrast to the control group managed with CHX, the HA group had a statistically significant lower adjusted bleeding index. It could be useful to use a combination treatment of HA 0.2 percent gel for the first two months and 0.2 percent CHX for months two through six. Genovesi A et al., compared the effectiveness of 0.12% Chlorhexidine (CHX) versus 0.12% CHX plus HA mouthwash on the healing of submerged single implant inoculation areas [20]. Surgical outcome variables, and plaque, gingival, and staining indexes were recorded. In the early stages of healing, antiedematous effect was shown by 0.12 percent CHX plus HA mouthwash in the sites of patients which had dental implants placed. Thus it was concluded that HA would be ineffective in as an antiplaque agent.

The administration of the relative abundance of peri-implantitis-related bacteria was lowered by HA, particularly early colonising bacteria, demonstrating that it has a specific action in the early stages of the disease. The relative abundances of non oral genera were unaffected by HA. The administration of HA in advanced stages of peri-implantitis decreased microbial alpha diversity, suggesting that the peri-implant site acts as a barrier to bacterial colonisation as was in the study by Soriano-Lerma A et al., [21].

Sánchez-Fernández E et al., examined how HA affected peri-implant clinical parameters and crevicular concentrations of the proinflammatory biomarkers Interleukin (IL)-1 and Tumour Necrosis Factor (TNF) in patients with peri-implantitis [22]. The participants in a randomised controlled experiment had peri-implantitis. Patients received either a 0.8% HA gel (test group), an excipient-based gel (control group 1), or no gel at all (control group 2). Observations were made after 0, 45, and 90 days of therapy. Enzyme-linked immunosorbent assays were used to determine the levels of IL-1 and TNF in crevicular fluid at baseline and 45 days following therapy. A total of 61 patients were divided into the test group, control group 1, or control group 2. At 45 days the PPD was significantly lower in the test group than in both control groups. At 90 days, there was a tendency for the test group to have less bleeding on probing than the control group 2 (p=0.07). At 45 days, implants with a PPD 5 mm in the control group 2 had higher levels of IL-1 than in the test group. This study showed for the first time that topical HA gel treatment may lower inflammation and IL-1 levels in crevicular fluid around implants with peri-implantitis and in the peri-implant pocket.

Use of HA in Surface Modifications of Dental Implants

In two groups of fifteen rabbits each, Mohammad MH and Al-Ghaban NM study used immunohistochemistry TNF estimate to assess the effects of HA on the bone-implant interface [23]. In both groups (experimental and control), 60 implants were implanted into the rabbits' tibias; the experimental implant, which was coated with 0.1 mL of HA gel, was injected into the left tibia. Immunohistochemical tests were performed to evaluate the TNF-α expression on both groups at all healing intervals. In fact, osteoclasts were observed in the second week with no discernible changes between the experimental and control groups, whereas the highest mean value of positive TNF expression was discovered for osteoblasts and osteocytes at week four for the experimental group. TNF-α inhibits osteoblast differentiation at various stages and can operate on the precursor of osteoblasts by promoting stem cell cellular differentiation. The early stages of postoperative healing showed an elevated positive expression of TNF-α in the experimental group, indicating an accelerated osseointegration for HA-coated implants. Histologically, both groups showed newly produced bone tissue, while the experimental group had a somewhat higher prevalence of both new bone and osteoid tissue.

Use of HA in Osseointegration of Dental Implants

Yazan M et al., evaluated ten New Zealand rabbits, 10-week-old and weighing 2.5-3.0 kg [24]. In the mandibular molar region, implant sites that were sufficiently spaced from the tooth apices were selected. Each rabbit had two cavities prepared: one anterior for the control implant and one posterior for the HA gel implant. Two months following the procedure, the new bone and osteoid matrix content around the dental implants were assessed histologically and histomorphometrically, and there was no discernible difference between the two groups.

Lorenz J et al., did a prospective investigation, to examine the regenerative capacity and routes of a novel beta-Tricalcium Phosphate (TCP) and HY-based Injectable Bone replacement (IBS) material for their potential use in alveolar bone regeneration within extraction sockets [25]. The author concluded that the IBS underwent a time-controlled breakdown and contributed to an osteoconductive tissue reaction. IBS contributed to a long-term stable insertion bed for dental implants, according to clinical and radiological follow-up examination of the implants placed in the regenerated area. The IBS appears as a bulk that develops within the augmentation bed and that, thanks to an osteoconductive technique, encourages the creation of new bone.

CONCLUSION(S)

The HA application appears to be a promising approach for treating different periodontal defects, according to studies. Furthermore, the use of autologous bone grafts in conjunction with esterified HA tends to be effective in accelerating new bone development in infra-bony defects and other regenerative procedures. More research may be needed to confirm the clinical benefits of using esterified HA to treat periodontal defects.

Acknowledgement

The authors gratefully recognise the significant assistance provided by the academics whose works are referenced in this study. The authors would also want to express their gratitude to the writers, editors, and publishers of all the books, journals, and articles that served as the foundation for this article.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 18, 2022
- Manual Googling: Oct 11, 2022
- iThenticate Software: Oct 17, 2022 (23%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 12, 2022**
Date of Peer Review: **Sep 19, 2022**
Date of Acceptance: **Oct 26, 2022**
Date of Publishing: **Feb 01, 2023**