

Sticky Science: Hyaluronic Acid and Its Role in Periodontal Management

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I.

II. INTRODUCTION

One of the most abundant glycosaminoglycans in the extracellular matrix is hyaluronic acid (HA), also known as hyaluronan [1]. Karl Meyer and John Palmer isolated HA from the cow's eye's vitreous fluid in 1934 [2]. "HA," which comes from the Greek word "hyalos," which means "glass," included two sugar molecules, one of which was uronic acid. In addition, there are several repeating disaccharide units in this linear polysaccharide [3]. Interestingly, a healthy adult weighing 70 kg has about 15 g of HA in their body (4). Since HA is synthesised by most human cells, it may be involved in a number of important biological activities. This data shows that HA has therapeutic potential [5]. Chronic inflammatory disorders are currently treated with HA. Interestingly, periodontal disease affects the periodontium and is an inflammatory condition. The extracellular matrix of the gingiva and the periodontal ligament require HA, which is scarce in the mineralised periodontal tissues of alveolar bone and cementum [4]. Due to the subsequent effect on HA receptors, which are involved in inflammation, angiogenesis, and cellular migration, wound healing is hastened after HA administration. Both the deeper periodontal tissues and the marginal gingiva get symptom relief by HA [6].

The ability of HA to heal wounds has also been applied to various periodontal therapies, including soft and hard tissue regeneration as well as non-surgical and surgical therapy. Furthermore, HA controls the exchanges between cells and the matrix and is essential for cell signalling and haemostasis. Additionally, HA contributes to the inflow and outflow of waste materials and nutrients [7]. HA's wide range of uses, which are outlined in this review, make it noteworthy that it may be utilised in periodontal research. For the review, no systematic search approach was used. Using a combination of the keywords "hyaluronic acid, periodontics, periodontal therapy, periodontal regeneration, and wound healing," an online search was conducted for research without a time limit.

PROPERTIES OF HA

Because of its physicochemical and biological characteristics, HA has a number of functions in the body. Basic structural responsibilities in the extracellular matrix and developmental regulation through influences on cell behaviour through tissue architecture and microenvironment control are only a few examples of these biological functions. Additionally, these HA activities directly affect gene expression through receptor-mediated mechanisms [8,9]. The

characteristics of HA are viscoelastic and hygroscopic. Following HA's absorption by an aqueous solution, hydrogen and nearby carboxyl and N-acetyl groups establish bonds, enabling HA to retain its structural stiffness through water retention [10].

HA alters the surrounding cellular and extracellular micro and macro environments by stopping gaps and protecting surfaces. When medium and lower molecular weight HA were utilised in large doses, the bacteriostatic activity of HA was at its peak [11]. HA has a non-immunogenic nature and is biocompatible. For cell seeding, two HA modifications that offer a gel-like structure and stiffness are esterification and cross-linking [12]. Additionally, HA has anti-inflammatory qualities. By removing prostaglandins, metalloproteinases, and other bioactive compounds, it carries out scavenging activities [12]. According to osmotic action, HA also has antioxidant and antioedematous qualities [13]. The granulation tissue matrix is stabilised by HA's ability to scavenge reactive oxygen species [14].

SYNTHESIS OF HA

In contrast to other glycosaminoglycans, HA is a negatively charged glycosaminoglycan. In mammals, HA synthesis takes place on the cellular plasma membrane, while glycosaminoglycan synthesis frequently takes place in the Golgi apparatus. Furthermore, three hyaluronan synthase isoenzymes (HAS1, 2, and 3) are involved in the synthesis of HA [7]. The molecular weight of HA is 103-104 kDa, its length is 2-25 μm , and it is free of sulphate groups [8]. The largest amounts of HA are found in tissues such as the umbilical cord, synovial fluid, and epidermis, whereas the lowest concentration is seen in blood serum [15]. Uridine diphosphate is released into the extracellular space by a membrane-bound protein found in plasma membranes, which also transports activated monosaccharides to glycosaminoglycan chains to form HA. Tissue HA turnover is caused by either local metabolism or lymphatic outflow into the circulatory system. HA has a tissue half-life of 12 hours to 2-3 days, depending on how it is removed [16].

HA IN WOUND HEALING

As a structural element of cartilage and other tissues, HA is involved in many physiological and biological functions. Interactions between HA and proteins rich in various glycosaminoglycan forms result in the production of proteoglycans. It

promotes the invasion of extracellular matrix and inflammatory cells, which aids inflammation. Therefore, HA shows promise in affecting cellular behaviour through altering the cell environment [16]. In order to promote tissue healing, HA is involved in a variety of cell processes, including identification, movement, and proliferation. This increases HA's vulnerability to tissue repair cell colonization[17]. HA has been utilised in medicine for many years in its highly pure form because of its physiochemical properties and lack of immunogenicity. Since HA maintains a lot of water, it influences and enhances tissue regeneration, which stops scabs and scars from forming [18,19]. According to some theories, HA promotes angiogenesis, which raises the bone matrix's capacity to mend wounds. HA exhibits both angiogenic and anti-angiogenic properties at low and high molecular weights [20]. HA with a high molecular weight promotes osteo-induction, or the formation of new bone, throughout the healing process [21]. The findings of earlier research showed that exogenous HA has positive effects on wound healing [22-24]. Additionally, HA is utilised as a dermal filler in cosmetic dermatology [25].

HA shows promise in tissue engineering since it is essential for cell motility, organogenesis, and development [26]. Two HA changes that give cell seeding its gel-like structure and rigidity are esterification and crosslinking. These biodegradable biopolymers promote the growth of mesenchymal stem cells, fibroblasts, and chondrocytes (27). Gingivitis has been treated using HA as a chemotherapeutic drug. Furthermore, HA is implicated in the osseointegration of dental implants [28]. HA may show promise as a biomaterial scaffold in directed bone regeneration and tissue engineering due to its bone induction capabilities [29]. Following HA therapy, Ibraheem et al. [30] showed enhanced wound healing in extraction socket wounds in 2022. A variety of microorganisms in the planktonic phase also showed dose-dependent bacteriostatic effect from HA[30]. Cell receptors interact with hylauronan to produce cell responses. It's noteworthy that HA signalling involves a wide variety of cell receptor types. In HA signalling, CD44 is the most prevalent receptor [32]. CD44 signalling is essential for wound healing because fibroblasts need CD44 to emigrate into the injured area [33]. Signalling is significantly influenced by the receptor for hyaluronan-mediated motility (RHAMM), commonly referred to as CD168. Tissue healing and inflammation depend on

RHAMM-hyaluronan interactions [34]. Additionally, lymphatic vessel endothelial hyaluronan receptor 1 regulates tissue hydration and other biochemical aspects through the lymphatic system's absorption of HA, and hyaluronan receptor for endocytosis is implicated in hyaluronan endocytosis [35,36]. Tissue metabolism, tissue haemostasis, and the innate immune response are all impacted by toll-like receptors [37]. The creation of defensins, which have antibacterial qualities and use regeneration impulses for cells, is triggered by toll-like receptors [38]. An essential component of HA signalling is the molecular weight of HA. Interestingly, with varying molecular weights, HA triggers distinct signalling pathways [39].

HA IN PERIODONTAL THERAPY

There are varying quantities of HA in the periodontium. The gingiva and periodontal ligament have higher values than the alveolar bone and cementum. Furthermore, elevated serum levels of HA in the circulation indicate a gingival crevicular fluid serum overload factor [40]. Because scaling and root planing (SRP) reduces the number of pathogens in the periodontal pocket and changes the microbiota to be less harmful, it has a good impact on periodontal parameters [41]. According to the findings of earlier research examining SRP in conjunction with non-mechanical therapy, the application of systemic or local antibacterial medications substantially enhanced clinical parameters [42, 43]. Not all forms of periodontitis, however, should be treated with systemic antibiotics. Systemic antibiotic use must be restricted since resistance can develop and unneeded medication interactions can happen. HA is used after SRP as an adjuvant therapy for patients with gingivitis and chronic periodontitis. HA treatment causes metalloproteinases, prostaglandins, and bioactive substances to decrease. This prevents tissue deterioration, which facilitates healing [44]. Sahayata et al. [45] employed 0.2% HA gel (Gengigel®) topically for gingivitis patients. This earlier study's findings showed that HA therapy improved gingival health, decreased gingival bleeding, and lowered gingival fluid flow [43, 44]. Additionally, the effects of HA on periodontal parameters in individuals with periodontitis were examined by Pilloni et al. [46]. Significant improvements in bleeding on probing were one way that the results of this earlier study showed that the HA group performed better than the non-HA group [46]. Furthermore, Pistorius et

al. [47] showed that after receiving HA, there were improvements in bleeding.

In patients with chronic periodontitis, Eick et al. [48] compared the effects of HA with SRP and SRP alone. According to the results of this earlier study, the SRP + HA group's reduction in probing pocket depth (PPD) was noticeably greater than that of the SRP alone group [48]. After HA treatment, improvements in healing, periodontal indices, and clinical attachment level (CAL) have been noted. Al-Shammari et al. [49] assessed the effects of SRP by itself and SRP + HA in individuals with chronic periodontitis in a split-mouth trial. After six and twelve weeks, the test group showed improvements in gingival indices, CAL, and PPD [49]. Additionally, Madkour et al. [50] evaluated the impact of HA in individuals receiving treatment for chronic periodontitis. Gingival index, PPD, and CAL levels improved in both groups, however the SRP + HA group experienced the greatest improvement in these measures [50], which is comparable to the findings of Al-Shammari et al. [49]. Additionally, a systematic study by Eliezer et al. [51] showed that HA has positive benefits on CAL growth, pocket depth reduction, and bleeding reduction on probing during both surgical and non-surgical periodontal therapy. HA increased keratinisation and enhanced CAL. Since HA encourages neovascularisation, treatment with injectable HA gel at different dosages improved papillary regeneration [52]. The interdental papillary fill was compared by Çankaya and Tamam following the injection of HA into the mandibular and maxillary jaws. The injection was administered until the gingiva turned white. Following three, twelve, and twenty-four months, the interdental area showed that the maxilla still had 54.21, 73.22, and 79.35% coverage, while the mandible still had 57.24, 71.40, and 78.71% coverage [52]. Hyaluronan functions as an antimicrobial and encourages fibroblast adhesion to the cementum. Sodium hyaluronate also improves chemical communication between cells. The guided tissue regeneration membrane (GTR) frequently contains sodium hyaluronate as a result [53].

In a clinical study, Vanden Bogaerde [54] investigated the clinical efficacy of esterified HA fibres in treating 18 periodontal abnormalities. The CAL increased by 2.8 mm and the mean PPD decreased by 5.8 mm at the 12-month follow-up [54]. Histological analysis of experimental mice revealed the development of new alveolar bone in bone lesions [55]. In 2022, Rodríguez-Aranda et al. conducted a systematic review and found that HA has positive effects on periodontal regeneration.

Using HA alone or in conjunction with bone transplant or other biomaterials improved radiographic parameters, CAL, PPD, and BOP, according to this systematic review [56].

III. CONCLUSION

HA is an essential biomaterial in periodontal therapy. Patients with implants, periodontal abnormalities, gingivitis, and periodontitis experience clinical improvements after receiving HA treatment. By speeding up the healing process, HA treatment improves postoperative outcomes and increases patient comfort. The therapeutic effects of HA in periodontal disease, however, need more investigation. This will also establish the precise applications, the best way to provide HA for treating periodontal diseases after surgery, and the possibility of full regeneration of periodontal tissue.

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