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From Healing to Aesthetics: Hyaluronic Acid in Dental Practice

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ABSTRACT: Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan with unique physicochemical properties that make it an essential component of extracellular matrices in various tissues. In dentistry, HA has garnered significant attention for its therapeutic potential due to its roles in tissue regeneration, inflammation modulation, and wound healing. Found abundantly in non-mineralized periodontal tissues, such as gingiva and periodontal ligaments, and in lower concentrations in mineralized tissues like cementum and alveolar bone, HA contributes to maintaining the structural integrity and function of these tissues. HA's bioactivity makes it a versatile agent for use in periodontal therapy, oral surgery, implantology, endodontics and other dental specialities. Its anti-inflammatory and antimicrobial properties enhance recovery, reduce infection risks, and improve patient outcomes. This review highlights the multifaceted applications of HA in dental practice, emphasizing its potential to revolutionize periodontal and restorative treatments.

KEYWORDS: acid, hyaluronic; regeneration; biocompatibility; hyaluronan.

INTRODUCTION

Hyaluronic acid (HA), also referred to as hyaluronan, is one of the most predominant glycosaminoglycans in the extracellular matrix[1] HA', as it originated from hyalos (meaning glass in Greek), possessed two sugar molecules, one of them being uronic acid. Moreover, this linear polysaccharide exhibits numerous repeating disaccharide units.[2] The polyanionic disaccharide units of glucuronic acid and N-acetyl glucosamine, which are joined by alternating bl-3 and bl-4 bonds, make up the structure of HA. It is found in the extracellular matrix of skin, vitreous humour, embryonic mesenchyme, connective tissue, synovial fluid, and several other human tissues and organs.[3] It plays a key role in numerous physiological and structural functions, such as facilitating cellular and extracellular interactions, interacting with growth factors, regulating osmotic pressure, and providing tissue lubrication. These functions collectively contribute to preserving the structural integrity and homeostasis of tissues. Comprehensive research on the chemical and physicochemical properties of HA, along with its physiological significance in humans, has established it as an excellent biomaterial for applications in cosmetics, medicine, and pharmaceuticals.[4]

HA is one of nature's most hygroscopic compounds. Adjacent carboxyl and N-acetyl groups generate hydrogen bonds when HA is added to an aqueous solution; this property enables HA to retain water and maintain conformational stiffness. Additionally, HA has significant viscoelastic properties that lessen the ability of bacteria and viruses to enter the tissue.[5] In both mineralised and non-mineralized tissues, the molecule plays a crucial role in the sequence of events known as the wound-healing process, which includes inflammation, granulation tissue creation, epithelium formation, and tissue remodelling.[6,7]

By controlling osmotic pressure and tissue lubrication, it maintains the structural and homeostatic integrity of tissues.

Advances in the development and use of HA-based biomaterials in the treatment of different inflammatory disorders have been made as a result of the several functionalities attributed to HA.[8] It is therefore possible that HA has comparable roles in the healing of the mineralised and non-mineralized tissues of the periodontium, given its multifunctional involvement in wound healing generally and the biological similarities between gingival and bone healing.[6,9] HA-based biomaterials are extensively studied in tissue engineering for their biocompatibility, biodegradability, and capacity to replicate the native

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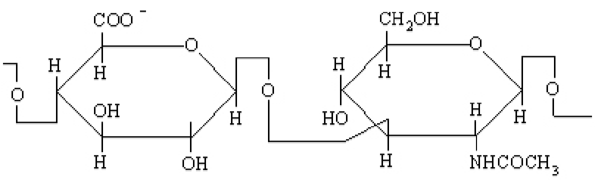
extracellular matrix (ECM). Crosslinked HA hydrogels find applications in cartilage regeneration, wound healing, and targeted drug delivery systems.[10]

HISTORY

HA is a high-molecular-weight biopolymer first identified in the vitreous humor of cow eyes by Karl Meyer and his assistant John Palmer at Columbia University in 1934. Today, HA is extensively used in medicine, dentistry, and cosmetics. In medicine, it is applied as a joint lubricant and as a filler for soft tissue augmentation. In cosmetics, it serves as a powerful moisturizer and anti-aging agent, helping to improve skin hydration, reduce the appearance of fine lines and wrinkles, and is even incorporated into hair care products. In the field of dentistry, preliminary clinical trials have been conducted by Pagnacco and Vangelisti in 1997.[11]

CHEMISTRY

The disaccharide consists of d-glucuronic acid (an uronic acid) and d-N-acetyl-glucosamine (an amino sugar), linked by alternating beta-1,4 and beta-1,3 glycosidic bonds (Figure 1). Both sugars are structurally related to glucose, and in their beta configuration, the bulky groups (such as hydroxyl groups, the carboxylate moiety, and the anomeric carbon of the adjacent sugar) are positioned in the sterically favourable equatorial orientation. Meanwhile, the smaller hydrogen atoms occupy the less sterically favourable axial positions. This spatial arrangement contributes to the energetic stability of the disaccharide structure.[12]



d-Glucuronic acid N-acetylglucosamine

Figure 1. Chemical structure of HA

PROPERTIES OF HA

Water Retention and Osmotic Balance

HA's hygroscopic nature allows it to retain large amounts of water, contributing to tissue hydration and maintaining osmotic pressure. This property is critical for providing structural support and lubrication in tissues such as skin, joints, and eyes.[13]

Joint Lubrication and Shock Absorption

In synovial fluid, HA forms a viscoelastic gel that reduces friction between articular cartilage surfaces and absorbs mechanical stress during movement. Its high viscosity makes it an effective shock absorber.[14]

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Anti-Inflammatory Effects

HA modulates inflammation by inhibiting the production of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and reducing the activity of inflammatory cells like neutrophils and macrophages. High-molecular-weight HA suppresses inflammation, while low-molecular-weight HA may act as a signalling molecule during tissue injury.[15]

Role in Wound Healing

HA promotes wound healing by enhancing fibroblast migration, proliferation, and collagen deposition. It also regulates angiogenesis and modulates the inflammatory response to accelerate tissue repair.[16]

Tissue Regeneration and Remodelling

As a key component of the extracellular matrix (ECM), HA provides a scaffold for cell attachment and migration, which is essential for tissue regeneration and remodelling. It also interacts with cell surface receptors like CD44 and RHAMM, influencing cell signalling pathways that regulate proliferation and differentiation. [17]

Anti-Aging and Skin Hydration

In the skin, HA binds water molecules to maintain hydration, elasticity, and turgor. It reduces transepidermal water loss and minimizes the appearance of wrinkles. Additionally, HA stimulates keratinocyte proliferation and enhances the skin barrier function.[18]

Immunomodulation

HA interacts with immune cells through receptors such as CD44 and TLR4, regulating immune responses and promoting tissue homeostasis. High-molecular-weight HA is anti-inflammatory, while fragmented HA (low-molecular-weight) can activate immune responses during injury or infection.[19]

Role in Angiogenesis

HA regulates blood vessel formation by modulating endothelial cell behaviour and promoting vascular endothelial growth factor (VEGF) expression. This is critical in wound healing and tumor growth.[20]

APPLICATIONS IN DENTISTRY

HA IN PERIODONTOLOGY

Soft periodontal tissues all depend on HA, as do hard tissues like cementum and alveolar bone. It serves a variety of physiological and structural purposes in these tissues. The high-molecular-weight HA produced by hyaluronan synthase enzymes in the gingiva, periodontal ligament, alveolar bone, and periodontal tissues can regulate the inflammatory response. During the early stages of periodontitis, low-molecular-weight HA seems to be particularly prevalent in patients' gingival tissues, perhaps as a result of bacterial enzymes (hyaluronidases).[21]

Hyaluronic acid (HA) is a crucial component of the periodontal ligament matrix and plays a key role in cell adhesion, migration, and differentiation through its interaction with HA-binding proteins and cell-surface receptors like CD44. It has also been investigated as a metabolite and diagnostic marker for inflammation in gingival crevicular fluid (GCF) and is recognized as an important factor in tissue growth, development, and repair.[22] Reactive oxygen species (ROS), including

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superoxide and hydroxyl radicals commonly observed in periodontal diseases, contribute to the breakdown of high-molecular-weight HA. These radicals are primarily generated by infiltrating polymorphonuclear leukocytes and other inflammatory cells during bacterial phagocytosis.[23]

Low-molecular-weight HA fragments are involved in signalling tissue damage and recruiting immune cells, whereas high-molecular-weight HA helps suppress the immune response, preventing excessive inflammatory exacerbations. Hyaluronic acid (HA) plays a vital role in periodontal treatment due to its anti-inflammatory, antibacterial, anti-edematous, and tissue-regenerative properties. Studies have shown that HA use can reduce pocket depth, improve attachment levels, and minimize bleeding on probing. Its antibacterial properties help combat periodontal infections, while its ability to reduce inflammation and promote tissue regeneration aids in restoring gum tissue to its natural position.

HA can be prepared as a gel or film and applied to the affected area to promote tissue regeneration and reduce inflammation. HA can be added to a mouthwash or rinse to help improve healing and reduce periodontal infections.[24] Jentsch H et al. demonstrated that a gel formulation containing 0.2% high-molecular-weight hyaluronic acid (HA) has a beneficial effect in the treatment of plaque-induced gingivitis, serving as an effective adjunct to scaling and root planing (SRP).[25]

Additionally, the use of 0.8% HA after comprehensive mechanical debridement has shown significant clinical benefits, including enhanced healing following non-surgical periodontal therapy.[26] A 0.2% hyaluronan gel has demonstrated significant benefits in treating plaque-induced gingivitis, including reduced peroxidase and lysozyme activity at 7, 14, and 21 days.[27] According to Ballini et al., autologous bone and an esterified low-molecular HA preparation appear to work well together to speed up the production of new bone in infra-bone defects.[28] It is also possible, nevertheless, that applying HA to periodontal wound sites could have positive effects on the healing of periodontal disease and the regeneration of periodontal tissue.[29]

HA can be applied in pocket reduction therapy by injecting it into periodontal pockets to decrease inflammation and stimulate tissue repair, resulting in improved attachment levels and reduced pocket depth. It is also beneficial in periodontal surgery, where it enhances healing and regeneration when applied topically or via injection. Its high water-binding capacity helps keep gums hydrated, supporting healing, while its ability to stimulate fibroblast proliferation further facilitates tissue regeneration.[30, 31]

Studies have demonstrated the efficacy of HA gel in reconstructing interdental papilla by enhancing soft tissue volume and reducing the visibility of black triangles. It works by stimulating collagen synthesis, hydrating the tissues, and improving overall gingival health. Clinical research indicates that HA gel, when injected directly into the papillary region, results in significant soft tissue augmentation, restoring the natural contour of the interdental papilla. This minimally invasive procedure also reduces inflammation, enhances wound healing, and supports the long-term maintenance of the reconstructed papilla. [32,33,34]

HA IN IMPLANT DENTISTRY

HA has been demonstrated to decrease implant failure rates and enhance osseointegration. According to studies, using HA can increase the amount of bone surrounding dental implants, which can boost the stability and endurance of the implant and extend its lifespan. Being one of the key glycosaminoglycans in the cellular matrix produced by fibroblasts, synoviocytes, and chondrocytes, HA's composition is linked to its sensible use. It also exhibits a notable decrease in inflammation during wound healing, favouring cell proliferation, re-epithelialization, and scar reduction.[35] HA functions as a coating on the migration, adhesion, proliferation, and differentiation of cell precursors on titanium implants by strengthening the bond between the implant and bone. Cervino et al. evaluated the biological ramifications in the early phases of healing and concentrated on adding HA to the implant surface.[36]

HA IN ORAL AND MAXILLOFACIAL SURGERY

Hyaluronic acid plays a significant role in enhancing wound healing by promoting tissue regeneration, reducing inflammation, and stimulating angiogenesis. It can aid recovery after oral procedures such as tooth extractions or implant placement surgeries. In cases requiring bone regeneration, HA has been shown to improve bone density and stimulate osteogenesis in the maxillofacial region, making it beneficial for surgeries involving bone grafting. Additionally, hyaluronic acid is widely used in the treatment of temporomandibular joint (TMJ) disorders. When injected into the joint space, it helps reduce inflammation, improves joint lubrication, and encourages tissue regeneration. Numerous studies in the literature highlight the effectiveness of hyaluronic acid in managing TMJ-related conditions.[37]

Additionally, hyaluronic acid (HA) has proven beneficial following third molar surgeries. Yilmaz et al. investigated the effectiveness of local HA administration after impacted third molar extractions, focusing on its impact on pain, swelling, and mouth-opening limitations.[38] Koray et al. showed that the HA spray as compared to benzydamine hydrochloride spray, was more effective in reducing edema, pain and trismus during the early postoperative period after the extraction of impacted mandibular third molars.[39]

HA IN PEDIATRIC AND PREVENTIVE DENTISTRY

Hyaluronic acid (HA) has proven to be a valuable tool in paediatric dentistry due to its biocompatibility, anti-inflammatory, antimicrobial, and tissue-regenerative properties. It is widely used for managing recurrent aphthous ulcers in children, providing pain relief, reducing inflammation, and accelerating healing. In cases of plaque-induced gingivitis, HA gels or sprays help reduce gingival bleeding and inflammation, promoting healthier gingiva. After tooth extractions, HA can be applied to the socket to minimize postoperative pain, swelling, and enhance tissue regeneration. HA supports the management of gingival inflammation caused by appliances such as space maintainers, improving patient comfort and tissue healing.[40]

Its antimicrobial properties also contribute to caries management, particularly in early childhood caries, by reducing bacterial growth. Additionally, HA is beneficial in treating soft tissue injuries caused by trauma or accidental bites, aiding in faster healing and preventing infections. Moreover, HA has shown promise as an adjunct in pulpotomy procedures, promoting pulp tissue repair and regeneration due to its anti-inflammatory and healing properties. These diverse applications make HA a valuable adjunct in paediatric dentistry, contributing to improved oral health outcomes in children.[41]

HA IN ORTHODONTICS AND DENTOFACIAL ORTHOPAEDICS

HA is known to modulate the extracellular matrix, promoting tissue remodelling, which is crucial during orthodontic adjustments. It has been applied topically to gingival tissues to reduce discomfort, promote faster healing, and improve tissue response to braces. Additionally, HA is used as a supportive treatment for temporomandibular joint disorders (TMDs), a common issue in orthodontic patients. The ability of HA to enhance collagen synthesis and stimulate fibroblast activity makes it a promising agent in improving the outcomes of orthodontic procedures. According to a study by Choukroun et al. (2018), HA treatment in the periodontal region following tooth movement significantly improved tissue regeneration and reduced post-treatment complications.[42] Another study by Sarrafian et al. (2020)demonstrated the effectiveness of HA in reducing the pain and inflammation associated with orthodontic tooth movement, making it a useful adjunct in clinical orthodontic practice. Overall, the application of HA in orthodontics offers promising benefits in enhancing tissue repair and improving patient comfort during orthodontic treatment.[43]

HA IN CONSERVATIVE DENTISTRY AND ENDODONTICS

In endodontic treatments, HA has been primarily used for its anti-inflammatory and wound-healing effects, particularly in managing periapical lesions and enhancing tissue regeneration after root canal procedures. HA is often utilized as a carrier for growth factors or stem cells to enhance tissue repair and regeneration, particularly in the context of pulp regeneration and revascularization. Studies, such as those by Saghiri et al. (2018), have demonstrated that HA can aid in improving the healing of periapical tissues and stimulate the regeneration of dentin-pulp complex. Additionally, HA's antimicrobial properties make it a promising adjunct in disinfecting the root canal system during treatment, thus reducing the risk of reinfection.[44]

Research suggests that HA irrigants can effectively remove debris and the smear layer from the root canal system without harming the pulp or dentin. Additionally, HA has been employed as a filler to address resorptive flaws and root perforations. Because of its biocompatibility and capacity to promote tissue regeneration, it is an excellent material for repairing these defects.[45]

FUTURE PERSPECTIVES

The future perspectives of hyaluronic acid (HA) in dentistry are promising, with ongoing research focusing on its expanded applications in both soft and hard tissue regeneration. In addition to its use in tissue regeneration, HA is being explored for its role in enhancing the outcomes of dental implants by promoting osseointegration and soft tissue healing around the implant site. HA-based formulations, including gels and sprays, are being developed for minimally invasive procedures, allowing for faster recovery and improved patient comfort. Furthermore, HA's potential as a carrier for growth factors and stem cells offers significant promise for dental pulp regeneration and the revascularization of necrotic teeth. Additionally, HA has great promise for dental pulp regeneration and the revascularisation of necrotic teeth due to its capacity as a carrier of growth factors and stem cells. Preventive, restorative, and regenerative dentistry are just a few of the dental practice areas that could undergo a revolution as a result of HA's adaptability and regeneration powers as research advances.

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