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Promising role of hyaluronic acid in periodontology

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Abstract

Hyaluronic acid is a naturally occurring linear polysaccharide found in connective tissue, synovial fluid, and other tissues' extracellular matrix. In medical fields such as orthopedics, dermatology, and ophthalmology, its use in the treatment of the inflammatory process is well-established. Hyaluronate has been shown to have anti-inflammatory, anti-edematous, and anti-bacterial properties in the treatment of gingivitis and periodontitis in dentistry. Its administration to periodontal wound sites could achieve comparable beneficial effects in periodontal tissue regeneration and periodontal disease treatment due to its potential role in wound healing modulation. It could be used as an adjunct to mechanical therapy in the treatment of periodontitis because of its tissue healing properties. This review article focuses on the importance and recent advancements of hyaluronic acid in the field of periodontics.

Keywords: hyaluronic acid, periodontitis, oral gel, hygroscopic, healing.

Introduction

The concept of using chemicals in treating oral diseases has been a widely accepted part of dental practice. But the usage of chemotherapeutic agents in treating periodontitis is a recent initiative. It is well proven that mechanical therapy alone provides an excellent clinical response in most of the patients of chronic periodontitis. But in certain patients, periodontal treatment strategy should aim not only to reduce bacterial load by mechanical therapy, but should also consider a combination of mechanical and chemical treatment which results in good recovery.[1]

Chemotherapeutic agents can be delivered topically to the exposed tooth surfaces and gingiva in the form of dentifrices, gels, mouth rinses and supragingival irrigants.[1] Local delivery of antimicrobial agents into the subgingival environment act as an adjunctive treatment option for periodontal diseases. As compared to systemically delivered drugs, the side effects and drug interactions are mostly nonexistent in case of locally delivered agents. Topical antimicrobial agents usually include Chlorhexidine, Tetracyclines and metronidazole. Hyaluronic acid (HA), which is an extracellular component of connective tissue, is a recent addition to the classification of local chemotherapeutic agents.

In the field of dentistry, preliminary clinical trials have been conducted by Pagnacco and Vangelisti in 1997.[2]

Hyaluronic acid has shown anti-inflammatory, anti-oedematose, and anti-bacterial effects for the treatment of periodontal disease, which is mainly caused by the microorganisms present in subgingival plaque. It has been found that the equilibrium between the free radicals/reactive oxygen species (ROS) and antioxidants is the major prerequisite for healthy periodontal tissue. Individuals suffering from the periodontitis might be at higher risk of developing other systemic inflammatory diseases like cardiovascular diseases and diabetes.[3]

The periodontal connective tissue consists of fibrillar structures like collagen, elastin fibers and reticular fibers, in an amorphous matrix of glycosaminoglycan. Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan or linear polysaccharide of higher molecular weight in the extracellular matrix of connective tissue, synovial fluid and other tissues. It is the most abundant glycosaminoglycan found in the extracellular matrix of soft periodontal tissues.[4] It has various physiological and structural functional roles, such as cellular and extracellular interactions, interactions with growth factors and regulation of the osmotic pressure and tissue lubrication. These functions help in maintaining structural integrity and homeostasis of the tissue. The use of HA has been established in various medical fields such as orthopedics, dermatology and ophthalmology. In the field of dentistry, hyaluronic acid has shown anti-inflammatory as well as anti-bacterial activities in gingivitis and periodontitis therapy. Its tissue healing properties makes it very useful to be used as an adjunct to mechanical therapy in the treatment of periodontitis.[5]

However, it is also conceivable that HA administration to periodontal wound sites could achieve beneficial effects in periodontal tissue regeneration and periodontal disease treatment.

A Basic Knowledge on Hyaluronic Acid

History

Hyaluronic acid was discovered in 1934 by Karl Meyer and his colleague John Palmer, scientists at Columbia University, New York, who isolated a chemical substance from the vitreous jelly of cow's eyes.[6] They proposed the name hyaluronic acid as it was derived from Greek word hyalos (glass) and contained two sugar molecules one of which was uronic acid. The first hyaluronan biomedical product, Healon, was developed in the 1970s and 1980s by Pharmacia and approved for use in eye surgery (i.e., corneal transplantation, cataract surgery, glaucoma surgery, and surgery to repair retinal detachment).[7]

In the late 1970s, intraocular lens implantation was often followed by severe corneal edema, due to endothelial cell damage during the surgery. It was evident that a viscous, clear, physiologic lubricant to prevent such scraping of the endothelial cells was needed.[8,9]

Since its discovery in the early 1930s, there has been an increased awareness concerning the biology of hyaluronic acid, it's signaling pathways and its role in the biomedical and cosmeceutical industry. Being an endogenous molecule, hyaluronic acid is biocompatible, bio degradable, and has strong mucoadhesive, visco elastic properties.

Properties of Hyaluronic Acid

Through its complex interactions with matrix components and cells, hyaluronan has multifaceted roles in biology utilizing both of its physicochemical and biological properties.

These biological responsibilities range from basic structural functions in the extracellular matrix to developmental regulation via effects on cellular behavior via tissue macro- and micro environment control, as well as direct receptor-mediated gene expression effects. It possesses unique hygroscopic and viscoelastic capabilities among extra cellular matrix compounds.[10]

Hygroscopic Nature

Hyaluronic acid is one of the world's most hygroscopic compounds. Hydrogen bonding between adjacent carboxyl and N-acetyl groups occurs when HA is absorbed into aqueous solution; this property allows hyaluronic acid to maintain conformational rigidity and retain water. Hyaluronic acid can bind up to 6 liters of water per gramme. It has functions in space filling, lubrication, shock absorption, and protein exclusion as a physical background material.[11]

Viscoelastic Properties

The material's viscoelastic qualities may impede virus and bacteria penetration, which is a property of great importance in the treatment of periodontal disorders. As a viscoelastic material, hyaluronan aids in periodontal regeneration by maintaining gaps and protecting surfaces.[12] Through recognition of its hygroscopic and viscoelastic nature, hyaluronic acid can influence the cell function that modify the surrounding cellular and the extracellular micro and macro environments.

Chemistry and Physiochemical Properties

HA is a non-sulphated GAG and is composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronic β (1→3) bond as shown in Figure 1.[13] HA forms certain stable tertiary complexes in aqueous solutions.[14] HA possesses a diversity of physicochemical features despite its simple composition, which includes no differences in sugar composition or branching points. Depending on their size, salt content, pH, and related cations, HA polymers come in a variety of topologies and forms.[15] HA is not covalently connected to a protein core, unlike other GAGs, although it can aggregate with proteoglycans.[16] HA encompasses a large volume of water giving solutions high viscosity, even at low concentrations.

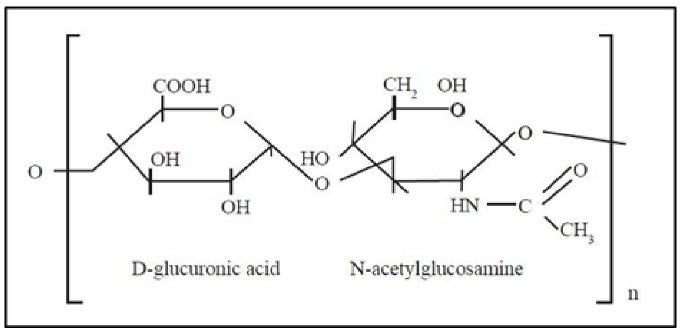

Figure 1: Chemistry of Hyaluronic Acid

Anti-inflammatory Properties

Exogenous Hyaluronan acts as a scavenger, draining prostaglandins, metalloproteinases, and other bioactive compounds, which may explain why HA has an anti-inflammatory impact.[17]

Anti-oedematous Properties

The anti-oedematous effect of HA may also be related to the osmotic activity. Due to its acceleration in tissue healing properties, it could be used as an adjunct to mechanical therapy.[18]

Antioxidant Properties

In a somewhat contradictory role, however, hyaluronan may regulate the inflammatory response, acting as an antioxidant by scavenging ROS. Thus, hyaluronan may help to stabilize the granulation tissue matrix.[19]

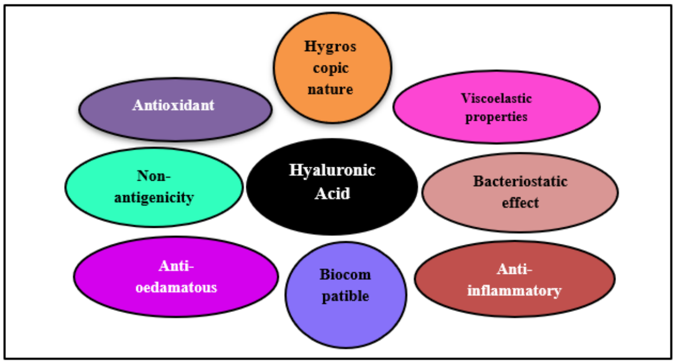

Figure 2: Properties of Hyaluronic Acid

Physiology of Hyaluronic Acid

Hyaluronic acid is a non-sulphureous component that is important for the structure and function of the extracellular matrix in a variety of tissues, including the vitreous corpus, synovial fluid, umbilical cord, synovial joints, skin (where it is a major component of the basal epidermis with a concentration of 55%), and oral mucosa, including mineralized and non-mineralized periodontal tissues. Hyaluronic acid has been found in varying amounts in all periodontal tissues, with non-mineralized tissues - gingiva and periodontal ligament - being more abundant than mineralized tissues - cement and alveolar bone.[20] Because of the high concentration of hyaluronic acid in blood serum, it is found in great quantities in the gingival fluid as a serum factor.[21]

Physiology of Hyaluronic Acid in Gingival Tissue

Endogenous hyaluronic acid is a naturally occurring biological material that is a key component of connective tissue matrix, particularly the gingiva. Its combination with other proteoglycans and collagen gives connective tissue's extracellular matrix stability and flexibility. Hyaluronic acid forms a viscous macro aggregate that regulates tissue hydration and enables the passage of substances in the interstitial space by creating hydrogen bonds with various proteins and water molecules.

Hyaluronic acid is capable of absorbing 50 times its dry weight in water. This compacts the tissue matrix, increasing small-molecule exchange and diffusion while also acting as a barrier to macromolecules and other invading substances. Hyaluronic acid works as a regulator of migration and cellular defense processes, which are particularly crucial in wound healing and tissue regeneration, when it attaches to cell receptors that are only present on active defense cells. CD44, a heparin-type proteoglycan containing sulphate that is specific for epithelial cells at the epithelial-mesenchymal border and regulates interactions between cells and the extracellular matrix, including their association with hyaluronic acid, is likely to bind to hyaluronic acid. In the presence of pathogenic bacterial flora, this same type of receptor is engaged in the interaction between gingival fibroblasts and T and B lymphocytes, and it can speed up the gingival immune response. The stimulation of fibroblasts with bacterial endotoxin increases its production. [22,23]

Uses of Hyaluronic Acid

HA is involved in a variety of physiological and biological processes. In cartilage and other tissues, it serves as a structural component. To produce proteoglycans, it connects with proteins that are rich in the other forms of glycosaminoglycans. Many cell processes, such as cell proliferation, recognition, and movement, are directly or indirectly associated to HA, which will contribute to its tissue healing properties.[24]

Because of its unique physiochemical properties and most importantly the non-immunogenicity of the highly purified form, Hyaluronan has already found medical applications for many years. Some important clinical applications are:

1. It is used as dermal filler in the field of cosmetic dermatology.[25]
2. Scar formation in the surgical wounds can be prevented by the administration of HA during surgery.
3. Many reports have attested to the effects of exogenous Hyaluronan in producing beneficial wound healing outcomes.[26]
4. In orthopedics, for treatment osteoarthritis of the knee and rheumatoid arthritis.[27]
5. In ophthalmology, for treatment of cataract and xeropthalmia.
6. In the field of tissue engineering, hyaluronan has also been studied. Because of its importance in organogenesis, cell migration, and overall development.

Oncology

The realm of oncology is another area where HA may be more commonly used. Many cancers have an elevated HA content in the stroma and adjacent tissue matrix, which can be problematic. In malignancies of epithelial origin, there is a particularly large increase in the level of HA (as stated by Kultti, as many as 87 percent cases of adenocarcinomas of the pancreas have a high expression of HA). In the vast majority of cases, this procedure is linked to a negative prognosis. This is owing to the fact that an increase in HA production is linked to apoptosis, treatment resistance, and invasiveness. Increased interstitial pressure is linked to an increase in HA in the tumor environment, which can lead to constriction of the supplying blood vessels' lumen. Hypoxia and medication resistance are the results of this condition. Aside from its physicochemical features, HA plays a critical role in tumor physiology, particularly through its action on tumor cell receptors. [28,29]

Ophthalmology

In ophthalmology, HA has a variety of applications, both conservative and operative. Due to its viscoelastic qualities, it is commonly employed as a "lubricant" component and is frequently used as the principal ingredient in artificial tear compositions for the alleviation of dry eye. It soothes inflammation, hydrates the eye, and restores sodium hyaluronate deficiency in the tear film. The chemical is frequently found in a form that is free of preservatives. Those who wear contact lenses need to use eye drops. Its unique qualities, such as tear film stability, reduced friction during blinking, and a significant reduction in hazardous chemicals attaching to the eye, significantly relieve dry eye symptoms. More than 50% of people cite dry eye the main reason for resignation from wearing contact lenses.[30]

Aesthetic dermatology

The most often used cosmetic filler is sodium hyaluronate (KH). Which has the role of filling and plumping up the extracellular tissue space. It's utilized to fill minor, superficial wrinkles and provide the skin elasticity and flexibility in liquid formulations, while cross-linked preparations are used to improve face features, model the breast in women, the thorax in males, and the buttocks. Correction of nasolabial folds and wrinkles, as well as mitigating horizontal forehead wrinkles, raising eyebrows, positioning the nose, changing the shape and volume of the lips, modelling the cheeks and chin, body contouring (enlargement and modelling of breasts, thighs, buttocks, and calves), and most recently improving the shape of the labia, can all produce excellent results (labiaplasty). Small volumes of HA are injected intradermally or subcutaneously to give approximately 6 months of fill effect. The drugstores also sell many creams and oral formulations containing KH but till now, no randomized studies have confirmed a positive, long-term smoothing effect on skin wrinkles using these methods.[31]

Role of Hyaluronic Acid in the Field of Period ontology

Hyaluronic acid is an important component of the human organism and is involved in almost all regenerative processes which take place in the human body. Hyaluronic acid is a major component of the extracellular matrix in almost all tissues. As such, its primary role is to bind water to permit the transportation of key metabolites and maintain tissue structure. Besides this hyaluronic acid have its various roles in gingival tissues, periodontal regeneration, periodontal wound healing, periodontal diseases and SRP (Scaling and Root Planing).

Hyaluronic Acid and Gingival Tissues

Endogenous hyaluronic acid is a naturally occurring biological substance that is a major component of connective tissue matrix, particularly the gingiva. Hyaluronic acid forms a viscous macro aggregate that regulates tissue hydration and allows the flow of substances in the interstitial space by forming hydrogen bonds with various proteins and water molecules.

Hyaluronic acid acts as a regulator of migration and cellular defense mechanisms, which are particularly important in wound healing and tissue repair, when it binds to cell receptors that are only present on active defense cells. CD44, a heparin-type proteoglycan containing sulphate that is specific for epithelial cells at the epithelial-mesenchymal border and regulates reactions between cells and the extracellular matrix, particularly their binding with hyaluronic acid, is likely to bind to hyaluronic acid. In the presence of pathogenic bacterial flora, this same type of receptor is involved in the interaction between gingival fibroblasts and T and B lymphocytes, and it can speed up the gingival immune response. The stimulation of fibroblasts with bacterial endotoxin increases its production. [32,33]

Hyaluronic Acid and Periodontal Regeneration

Inflammation, granulation tissue formation, and epithelium remodelling are all processes that hyaluronic acid plays a role in during the healing of chronic injuries in both mineralized and non-mineralized periodontal tissues.[34] In the early stages of inflammation, hyaluronic acid plays a number of roles, including providing a structural framework by interacting with fibrin plugs, which modulates inflammatory cell infiltration from the host's extracellular matrix. Hyaluronic acid also causes fibroblasts, keratinocytes, cement oblasts, and osteoblasts[35] to produce a series of polypeptide molecules (pro-inflammatory cytokines), which promotes the inflammatory response and, as a result, stimulates hyaluronic synthesis by blood vessel endothelial cells.[36] Hyaluronic acid is still involved in the activation of inflammatory cells like polymorphonuclear leukocytes and macrophages, as well as their migration and adherence at the site of injury, phagocytosis, and microbial pathogen destruction.

HA accelerates the bone regeneration by means of chemotaxis, proliferation and successive differentiation of mesenchymal cells. HA shares bone induction characteristics with osteogenic substances such as bone morphogenetic protein-2 and Osteopontin.[37]

Hyaluronic Acid and Periodontal Wound Healing

The chemoattraction of cells that accumulate and debride the injured tissue, foreign material, and microbial cells initiates a series of highly reproducible and rigidly controlled biologic events (inflammation, granulation tissue formation, epithelium formation, and tissue remodelling) that begin with chemoattraction of cells that accumulate and debride the injured tissue, foreign material, and microbial cells as shown in Figure 3. The formation and maturation of new extracellular matrix, which restores tissue resistance to functional stress, culminates these events.[38]

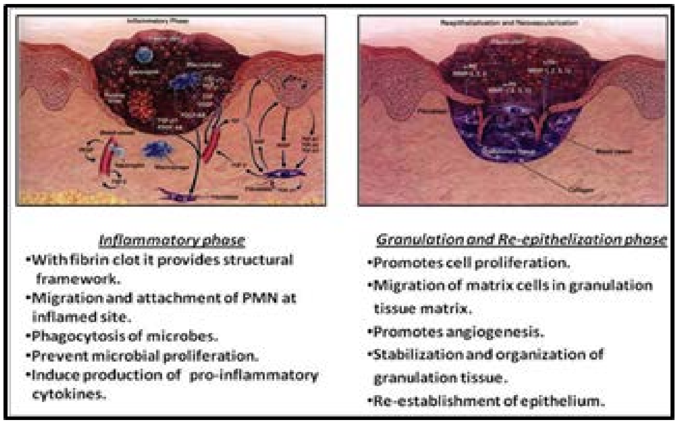

Figure 3: Role of hyaluronic acid in wound healing

Hyaluronic Acid and Periodontal Diseases

Periodontal tissue is a unique complex in which the non-mineralized gingival epithelium and other mineralized tissues form a union at the Cementoenamel Junction (CEJ). Maintaining the integrity of the union is critical for providing an effective barrier against microbial invasion and preventing bacterial toxins, enzymes, and other agents from destroying deeper periodontal tissues like the periodontal ligament, cement, and alveolar bone. Chronic inflammation associated with periodontal disease has harmed the structural integrity of the union, with such developments having harmful effects on the extracellular matrix of the deeper periodontal tissues, including collagen, proteoglycans, and hyaluronic acid. HA is an essential component of the periodontal ligament matrix and plays various important roles in cell adhesion, migration and differentiation mediated by the various HA binding proteins and cell-surface receptors such as CD44.[39] HA has been studied as a metabolite or diagnostic marker of inflammation in the gingival crevicular fluid (GCF) as well as a significant factor in growth, development and repair of tissues.[40]

Safety Protocol

Hyaluronic acid is biocompatible and intrinsically safe to use, with no evidence of cytotoxicity has been found.[41] Hyaluronic acid gel, injections or oral (by mouth), should not be used in patients with allergies.

Adverse Effects of Hyaluronic Acid

The side effects (not severe) of hyaluronic acid includes:

- Bruising
- Swelling
- Redness
- Pain
- Itching
- Tenderness at the injection site.

Hyaluronic Acid as a Toothpaste, Mouthwash and Oral Gel

HA has shown various anti-inflammatory, bacteriostatic and anti-plaque properties, due to which in the recent advancements and developments of new formulation of toothpastes, mouthwashes and oral gels, inclusion of HA is observed.

Hyaluronic Acid as Toothpaste

In various studies that were conducted, HA has been formulated in dentifrice as a wetting agent. The composition of toothpastes consists of remineralizing ingredient known as, nano-hydroxyapatite (nHAP). On addition of HA to dentifrice, showed increase in the activity of nHAP at various concentrations, hence concluding that there is a significantly higher remineralization of teeth when HA is added.

Hyaluronic Acid as Mouthwash

HA has been seen in combination with quaternary ammonium compound with a broad- spectrum antimicrobial activity like Cetylpyridinium chloride (CPC).[36] A novel mouth rinse combining Cetylpyridinium chloride and hyaluronic acid, has shown similar effects to chlorhexidine (CHX) in preventing accumulation of plaque. This mouthwash combination has shown synergistic effects and seems to be promising if ever used as regular home mouthwashes.[42]

Hyaluronic Acid as Oral Gel

HA has shown significant results when used as an adjunct to scaling and root planning (SRP) in gel form. In the present era, demand of esthetics has increased. So, construction of interdental papilla, especially in the esthetic zone, which appears as “black triangles”, is one of the most challenging tasks. Interdental “black triangles” were considered as the third most disliked and less attractive esthetic problem after caries and crown margins.[43] Various economically feasible injectable form of hyaluronic acid (HA) gel in various concentrations like, 1%, 2%, 5% HA etc. have been evaluated for finding their efficacy in the enhancement of deficient interdental papilla.

Metronidazole is a synthetic composite derivative of nitroimidazole class of antibiotic that restricts with bacterial DNA synthesis, causing cell death.[44] Hyaluronic acid in combination with metronidazole (MTZ) in gel form is observed to have positive effects in chronic periodontitis cases. A local type of metronidazole present in gel form usually forms reversed hexagonal liquid crystals when coming in contact with gingival crevicular fluid (GCF).[45] This retains the medicine sub gingivally for long durations by preventing the gel from facile exit outside the periodontal pocket. Topical application of sub gingivally hyaluronic acid gel can be used as an antimicrobial agent as an adjunct to root surface debridement and in addition, it also has osteoinductive properties.[46]

Future Perspective of Hyaluronic Acid in Periodontics

Hyaluronic acid is a naturally occurring component that is found throughout the body (50 percent in the skin) and has excellent moisturizing and re-modelling properties. Hyaluronic acid is constantly renewed due to its half-life of less than one day (50 percent of total hyaluronic acid is degraded in less than a day). Today, HA is widely used in many fields of medicine, including dentistry, for the treatment of acute and chronic inflammatory diseases. Clinical studies have shown good results and a high level of patient tolerance and acceptability, indicating the clinical value of hyaluronic acid in the treatment and management of gingival disease.[47] It is clear that it serves a more functional purpose in the treatment of chronic changes, such as those caused by periodontal disease. Hyaluronic acid appears to be a promising candidate as a mediator of periodontal tissue regeneration and treatment, promoting rapid symptom remission not only in the marginal gingiva, but also in deeper periodontal tissues, according to preliminary evidence.[48]

Future research and technological advancements are needed to improve the oral use of HA, such as studies on mucosal adsorptive phenomena, signage-size dependency, and intestinal and systemic effects of crosslinked HA. Nanotechnology must also be taken into account because it is a promising tool for creating stabilized and sized formulations that can interact with specific receptors and promote differentiated signals.

Summary and Conclusion

Hyaluronic acid is a naturally occurring component that can be found throughout the body (50 percent in the skin) and has excellent moisturizing and remodelling properties. Hyaluronic acid appears to be a promising candidate as a mediator of periodontal tissue regeneration and treatment, promoting rapid symptom remission not only in the marginal gingiva, but also in deeper periodontal tissues, according to preliminary evidence. Hyaluronan plays a multifunctional role in wound healing, and it's possible that a similar healing mechanism exists in periodontal tissues. Advances have been made in the development and application of Hyaluronan-based biomaterials in the treatment of various inflammatory conditions as a result of the many functions attributed to Hyaluronan during wound healing. However, more research into the therapeutic effects of hyaluronic acid in periodontal disease is needed to determine the true benefits of its use and the full realization of periodontal tissue regeneration.

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