Hyaluronic Acid - A Boon To Periodontal Therapy

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Abstract:

Hyaluronic acid is a naturally occurring linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, and other tissues. Its use in the treatment of the inflammatory process is established. In the field of dentistry, hyaluronic acid has shown anti-inflammatory and anti-bacterial effects in the treatment of periodontal diseases. Due to its tissue healing properties, it could be used as an adjunct to mechanical therapy in the treatment of periodontitis. Further studies are required to determine the clinical efficacy of hyaluronic acid in healing of periodontal lesion. The aim of the present review, article is to discuss the role of hyaluronic acid in periodontal therapy.

Keywords: *Gingivitis and periodontitis, Hyaluronic acid, Periodontal healing*

Background:

Periodontal diseases are one of the biggest reasons for tooth loss. Periodontitis is an inflammatory disease of the periodontium which elicits an immune response resulting in the loss of supporting structures of the teeth [1]. It is present in all age ranges of population from children to the elderly. The usual modes of treatment for periodontitis include informing the patient of the disease, oral hygiene instructions, scaling and root planning, periodontal surgery if indicated and in some cases the administration of systemic and local chemotherapeutic agents [2]. However, the final success rate of the treatment depends upon the status and maintenance of oral hygiene.

The periodontal connective tissue contains fibrillary structures like collagen, elastic fibres and reticular fibres in an amorphous matrix of glycosaminoglycan. Hyaluronic acid (HA; synonyms- Hyaluronan, Hyaluronate) is the most abundant glycosaminoglycan of higher molecular weight in the extracellular matrix of soft periodontal tissues [3]. It fulfills a variety of functions that are vital to the maintenance of healthy periodontal ligament. Hyaluronic acid was isolated from the vitreous body of the eye by Karl Meyer about 70 years ago. The classical sources for its isolation, besides the vitreous body, have been joint fluid, umbilical cord, rooster comb and certain strains of streptococci. It is synthesized in the plasma membrane of fibroblasts and other cells by the addition of activated monosaccharide to the reducing end of the polysaccharide polymer [4].

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Introduction:

Hyaluronic acid (HA) is a naturally occurring linear polysaccharide of the extracellular matrix of connective tissue, synovial fluid, and other tissues. It possesses various physiological and structural functions, which include cellular and extracellular interactions, interactions with growth factors and regulation of the osmotic pressure, and tissue lubrication. All these functions help in maintaining the structural and homeostatic integrity of the tissue. Extensive studies on the chemical and physicochemical properties of HA and its physiological role in humans have proved that it is an ideal biomaterial for cosmetic, medical, and pharmaceutical applications.

In the field of dentistry, preliminary clinical trials have been conducted by Pagnacco and Vangelisti in 1997[5]. HA has shown anti inflammatory, anti oedematous, 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 [6]. While, Pendyala *et al*. found that the total antioxidant capacity is inversely proportional to the severity of inflammation and can be used as a useful marker of periodontitis in health and diabetic patients [7]. However, it is also conceivable that HA administration to periodontal wound sites could achieve beneficial effects in periodontal tissue regeneration and periodontal disease treatment [8].

History

HA was discovered in 1934 by Meyer *et al.* John Palmer, scientists at Columbia University, New York, who isolated a chemical substance from the vitreous jelly of cow's Eyes [9]. They proposed the name HA as it was derived from the Greek word hyalos (glass) and contained two sugar molecules one of which was uronic acid. At the time, they did not know that the substance which they had discovered would prove to be one of the most interesting and useful natural macromolecules.

Chemistry:

Hyaluronic acid (HA) is naturally occurring non sulphated glycosaminoglycan with high molecular weight of 4,000-20,000,000 daltons. The precise chemical structure of HA contains repeating units of d glucoronic acid and *N*–acetyl d glucosamine. The primary structure of the polysaccharide comprises of an unbranched linear chain with the monosaccharides linked together through alternating â1,3 and â1,4 glycosidic bonds. The structural formula of HA has been explained in Figure 1. Most cells of the body are capable of synthesizing hyaluronic acid and synthesis takes place in the cell membrane. Hyaluronan binds to many other extracellular matrix molecules, binds specifically to cell bodies through cell surface receptors, and has a unique mode of synthesis in which the molecule is extruded immediately into the extracellular space upon formation [10].

Properties of HA:

HA has unique physiochemical and biological properties, which makes it useful in the treatment of the inflammatory process in medical areas such as orthopedics, dermatology, and ophthalmology [Figure 2].

Hygroscopic nature

HA is one of the most hygroscopic molecules known in nature. When HA is incorporated into aqueous solution, hydrogen bonding occurs between adjacent carboxyl and N acetyl groups; As a physical background material, it has functions in space filling, lubrication, shock absorption and protein exclusion [11].

Viscoelastic properties

Hyaluronan as a viscoelastic substance assists in periodontal regenerative procedures by maintaining spaces and protecting surfaces. Through recognition of its viscoelastic nature, HA can influence the cell functions that modify the surrounding cellular and the extracellular micro and macro environments. The viscoelastic properties of the material may slow the penetration of viruses, and bacteria, a feature of particular interest in the treatment of periodontal diseases [11].

Bacteriostatic effect

Recent studies on regenerative surgical procedures indicate that reduction of bacterial burden at the wound site may improve the clinical outcome of regenerative therapy. The high concentration of medium and lower molecular weight HA has the greatest bacteriostatic effect, particularly on *Aggregatibacter actinomycetemcomitans*, *Prevotella oris* and *Staphylococcus aureus* strains, which are commonly found in oral gingival lesions and periodontal wounds. A clinical application of HA membranes, gels, and sponges during the surgical therapy may reduce the bacterial contamination of surgical wound site, thereby, lessening the risk of postsurgical infection and promoting more predictable regeneration [12] .

Biocompatibility and non antigenicity

The highly biocompatible and non immunogenic nature of HA has led to its use in a number of clinical applications, which include: The supplementation of joint fluid in arthritis; as a surgical aid in eye surgery; and to facilitate the healing and regeneration of bone, surgical wounds and periodontal tissue. Modifications to Hyaluronan include esterification and cross linking to provide some structure and rigidity to gel for cell seeding purposes. These biopolymers are completely biodegradable and support the growth of fibroblasts, chondrocytes and mesenchymal stem cells.

Antiinflammatory

HA has the anti inflammatory effect, which may be due to the action of exogenous Hyaluronan as a scavenger by draining prostaglandins, metalloproteinases and other bio active molecules [13].

Antioedematous

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 [14].

Antioxidant

In a somewhat contradictory role, however, hyaluronan may regulate the inflammatory response, acting as an antioxidant by scavenging reactive oxygen species (ROS). Thus, hyaluronan may help to stabilize the granulation tissue matrix [15].

Functions and Uses of HA

HA has a lot of important physiological and biological functions. It plays a structural role in cartilage and other tissues. It associates with proteins that are enriched in the other types of glycosaminoglycans to form proteoglycans. HA is directly or indirectly related to many cell functions like cell proliferation, recognition, and locomotion, which will contribute to its tissue healing properties [16]. 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.
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.
4. In orthopedics, for treatment osteoarthritis of the knee and rheumatoid arthritis.
5. In ophthalmology, for treatment of cataract and xeropthalmia.
6. Hyaluronan has also been explored in the field of tissue engineering. Because of its significant role during organogenesis, cell migration and development in general.
7. Modifications to Hyaluronan include esterification and cross linking to provide some structure and rigidity to gel for the cell seeding purpose.
8. More recently, HA has been investigated as a drug delivery agent for various routes of administration, including ophthalmic, nasal, pulmonary, parenteral, and topical [16].

Hyaluronan has many structural and physiological functions within tissues, including extracellular and cellular interactions, growth factor interaction and in the regulation of osmotic pressure and tissue lubrication, which help maintain the structural and homeostatic integrity of tissues [17].

Modulation of inflammation

In the initial stages of inflammation:

- Enhanced inflammatory cell and extracellular matrix cell infiltration into the wound site
- Elevation in proinflammatory cytokine production by inflammatory cells and extracellular matrix cells.
- Organization and stabilization of granulation tissue matrix.

- Scavenges reactive oxygen species, such as superoxide radical ($\cdot O_2$) and hydroxyl radical ($\cdot OH$) thus preventing periodontal destruction.
- Inhibition of inflammatory cell-derived serine proteinases.

Stimulation of cell migration, proliferation and differentiation

The remarkable hydrophilicity of the hyaluronic acid makes the coagulum more receptive and thus more likely to undergo colonization by the cells committed to the reconstruction of the damaged tissue by migration, proliferation and differentiation of mesenchymal and basal keratinocytes [18].

Effect on angiogenesis

Low molecular weight hyaluronic acid has a marked angiogenic effect whereas, surprisingly, high molecular weight has the opposite effect.

Osteoconductive potential

Hyaluronic acid accelerates the bone regeneration by means of chemotaxis, proliferation and successive differentiation of mesenchymal cells. Hyaluronic acid shares bone induction characteristics with osteogenic substances such as bone morphogenetic protein-2 and osteopontin.

Carrier function

Hyaluronic acid may act as biomaterial scaffold for other molecules, such as BMP-2 and PDGF-BB, used in guided bone regeneration techniques and tissue engineering research [19].

Role of hyaluronic acid in the treatment of periodontitis

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. 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.

Based on current evidence in literature, it is now known that along with mechanical therapy, use of chemotherapeutic agents provide a better treatment strategy. The most common chemotherapeutic agents are antimicrobials and anti inflammatory drugs. They are administered either systemically or topically. Topical antimicrobial agents for the treatment of periodontal diseases include chlorhexidine, tetracyclines, and metronidazole. HA is a recent addition to the local chemotherapeutic agents. It has shown a number of clinical therapeutic properties.

Role of HA in Periodontal Wound Healing

Healing of periodontal wound includes a series of highly reproducible and rigidly controlled biologic events (inflammation, granulation tissue formation, epithelium formation and tissue remodelling) which begin with chemo attraction of cells that accumulate and debride the injured tissue, foreign material, and microbial cells . These events end with the formation and maturation of new extracellular matrix that restore resistance of tissue to functional stress.

Inflammatory phase

Hyaluronan has numerous roles in the initial inflammatory stages such as the provision of a structural framework via the interaction of Hyaluronan with the fibrin clot, which modulates host's inflammatory and extracellular matrix cell infiltration into the inflamed site**.** Hakansson *et al*. suggested role of Hyaluronan in migration and adherence of polymorphonuclear leukocytes and macrophages at the inflamed site and the phagocytosis and killing of invading microbes**.** Such events would allow counteraction of colonization and proliferation of anaerobic pathogenic bacteria in the gingival crevice and adjacent periodontal tissues. Hyaluronan itself may also prevent periodontal pathogen colonization by directly preventing microbial proliferation**.** Hyaluronan may also indirectly act to moderate inflammation and stabilize the granulation tissue by preventing degradation of the extracellular matrix proteins by serine proteinases derived from inflammatory cells as healing progresses. Hyaluronan also induces the production of proinflammatory cytokines by fibroblasts, keratinocytes, cementoblasts and osteoblasts which promote the inflammatory response and consequently stimulate hyaluronan synthesis by endothelial cells [20].

Granulation phase and reepithelisation

During granulation phase, Hyaluronan promotes cell proliferation, migration of matrix cells into granulation tissue matrix and granulation tissue organization. In non mineralized inflamed tissues, Hyaluronan is transiently elevated during the formation of granulation tissue and the re establishment of the epithelium. During the granulation tissue phase, HA in mineralized tissues is gradually replaced by a provisional mineralized callus. In later stage of the granulation phase, Hyaluronan synthesis ceases and existing Hyaluronan is depolymerized by hyaluronidases resulting in the formation of lower molecular weight Hyaluronan molecules and an alteration in the composition of the granulation tissue. Low molecular weight Hyaluronan fragments formed following hyaluronidase activity promote the formation of blood vessels (angiogenesis) within wound sites, although the precise mechanism of action is unknown.

Bone regeneration

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.

Effect on angiogenesis

It has been found that low molecular weight HA has marked angiogenic effect whereas, surprisingly, high molecular weight has the opposite effect.

Conclusion

It is evident that Hyaluronan has a multifunctional role in the wound healing process with a similar mechanism of healing potentially existing within periodontal tissues. As a consequence of the many functions attributed to Hyaluronan during wound healing, advances have been made in the development and application of Hyaluronan based biomaterials in the treatment of various inflammatory conditions**.** Hence, further long term longitudinal studies with certain standards such as application time, quantity of application, different forms and concentration needs to be carried out to understand therapeutic effect of HA in a better way.

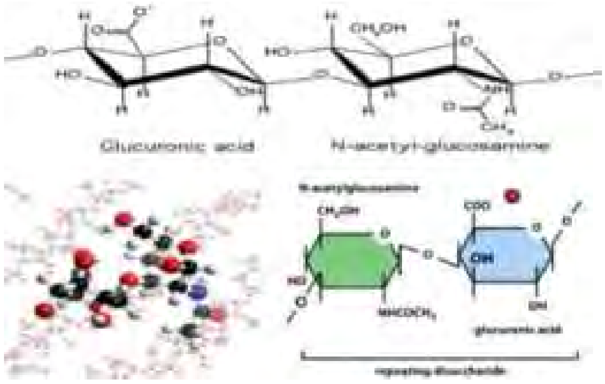

Figure 1: Structure of Hyaluronan.

Figure 2: Properties of Hyaluronic Acid

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