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# A Long Journey of Hyaluronic Acid (HA) in Dentistry–A Review

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**ABSTRACT**: Karl Meyer and John Palmer made the initial discovery and isolation of hyaluronic acid (HA), often referred to as hyaluronan or hyaluranate, from the vitreous body of cows' eyes in 1934. The Greek word "hyalos," which means glass, and uronic acid were combined to create the proposed term "hyaluronic acid." The only glycosaminoglycan (GAG) that is not produced in the Golgi apparatus is HA, which is also the most basic GAG. The human body produces hyaluronic acid (HA), a naturally occurring biopolymer (mucopolysaccharide) with significant biological roles. A sulfur-free sulphur glycosaminoglycan is called HA. Different HA fragment sizes have distinct effects. For example, high molecular weight hyaluronic acid, or HMWHA, has anti-inflammatory and immunosuppressive qualities, while low molecular weight hyaluronic acid, or LMWHA, is a powerful pro-inflammatory molecule. HA may be given to post-extraction wounds because of its positive effects on tissue regeneration and wound healing, which could impact the healing process and further improve quality of life. Applications of Hyaluronic Acid: Considering its physico-chemical characteristics, safety profile, biocompatibility, and biological functions, HA has a wide range of uses. The application of HA and its derivatives in the fields of medicine, pharmacy (e.g., drug delivery systems), nutrition (nutraceuticals, Nutri cosmeceuticals), urology, soft tissue regeneration, cancer therapy, pneumology, odontology, ophthalmology, urology, wound treatment, etc. Saliva, cementum, and alveolar bone have lower concentrations of HA than the gingiva and periodontal ligament, which contain the majority of HA in the oral tissues. Due to its inherent biocompatibility and widespread availability in bodily tissues, HA is a popular choice for tissue engineering, drug delivery, and illness treatment.

## I. INTRODUCTION

Dental support, phonetics, aesthetics, masticatory capacity, osseointegration, and denture stability are all significantly impacted by bone loss [1]. In these situations, bone grafts and/or biomaterials may be required to ensure that patients receive the proper oral rehabilitation. Hyaluronic acid (HA), sometimes referred to as sodium hyaluronate (HY) or hyaluronan (HYA), is one such substance that is widely found in the human body [2].

High molecular weight glycosaminoglycan (GAG) with repeating disaccharide non-sulfated units of N-acetylglucosamine and D-glucuronic acid makes up HA. As one of the main elements of the extracellular matrix and an extensively dispersed biomolecule in many tissues, including skin, synovial fluid, cartilage, tendons, eyes, and most bodily fluids, it is a biomolecule of great significance [3]. Hypoxic acid (HA) is an essential constituent of the extracellular matrix, which is required for multiple biological processes, including wound healing [4].

A kind of non-sulfated glycosaminoglycan known as hyaluronic acid (HA) is made up of linear polysaccharides found in the extracellular matrix of connective tissue, synovial fluid, and other bodily tissues and organs. Oral tissues, including hard periodontal tissues like cementum and alveolar bone, and soft periodontal tissues like gingiva and periodontal ligament, are rich in HA, an important component [5]. Due to its distinct physiochemical and biological characteristics, HA is helpful in treating inflammation in a variety of medical specialities, including dentistry, ophthalmology, dermatology, and orthopaedics [6]. When it comes to a variety of applications, including anti-inflammatory, bone regeneration, wound healing, oral ulcer, tissue regeneration, immunological modulation, anti-cancer, anti-diabetic, anti-aging, cosmetics, and skin restoration, HA is a chemical that truly is multipurpose [7].

Hyaluronic Acid's journey started a long time ago in the dental and general medical fields. On the other hand, very little is known about the uses of HA in dentistry. Therefore, the purpose of this review study was to go over the characteristics, uses, and changes made to HA in dentistry.

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**HISTORY**: In 1934, researchers at Columbia University in New York, Karl Meyer and John Palmer, identified HA by isolating a chemical compound from the vitreous jelly of cow's eyes. Since it comprised two sugar molecules, one of which was uronic acid, and was derived from the Greek word hyalos (glass), they suggested naming the product HA. [8]

**CHEMICAL STRUCTURE**: N-acetyl-d-glucosamine and d-glucoronic acid repeating units make up the exact chemical structure of HA. The monosaccharides are connected to one another by alternating β1,3 and β1,4 glycosidic linkages, forming the polysaccharide's main structure, which is an unbranched linear chain. [Figure 1] [9].

HA keeps the extracellular matrix (ECM) in its viscoelastic shape and moisturises the tissues [10].

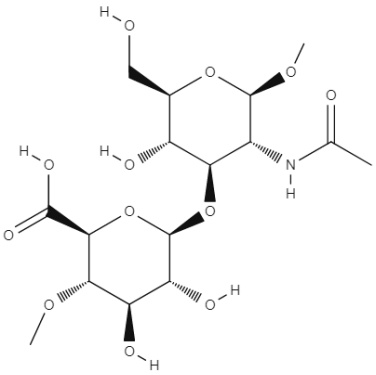

Fig1: Chemical structure of hyaluronic acid [ Source:Rigo D, da Silva LM, Fischer B, Colet R, Dallago RM, Zeni J. Hyaluronic Acid – from Production to Application: A Review. Bio Interface Res Appli Chem 2023;3(3):1-22.]

Because HA-based nanoparticles may self-assemble into a hydrophilic outer layer of HA and several hydrophobic nuclei, they can specifically target tumour tissues. In addition, NPs-HA exhibits superior accumulation at the tumour site in comparison to HA derivatives that are soluble in water.

## II. PROPERTIES OF HA

By influencing angiogenesis, hyaluronic acid (HA) stimulates osteoblasts' capacity to produce osteoblasts. Most human tissues, including soft connective tissue, joint synovial fluid, the lung, kidney, brain, and muscle tissue, contain hyaluronic acid (HA), also known as hyaluronan or hyaluronate[11]. It has been demonstrated that HA influences angiogenesis and can increase osteoblasts' ability to produce osteoblasts by encouraging mesenchymal cell migration and differentiation [12]. As HA is highly biocompatible and has low immunogenicity, it is particularly helpful when compared to other growth factors or scaffolds used in the process of bone healing [13]. These benefits have highlighted HA's potential as a top-notch material for bone repair.

**1. Hygroscopic nature**: Among the chemicals that are most hygroscopic are those that contain HA. An aqueous solution can hold onto water while remaining conformationally rigid when HA is added. This biological substance serves as a space-filling, lubricating, shock-absorbing, and protein-exclusion agent [14]. Adjacent carboxyl and N-acetyl groups form hydrogen bonds when HA is added to an aqueous solution. One gramme of HA may bind up to six litres of water, demonstrating the ability of HA to sustain conformational stiffness and water retention [15].

**2. Viscoelastic properties**: By altering cellular activity, HA can have an impact on extracellular and cellular micro and macroenvironments. Periodontal disorders are greatly impacted by the viscoelastic properties of HA, which may limit the entry of bacteria and viruses [16]. Because hyaluronan is a viscoelastic material, it aids in periodontal regeneration processes. By preserving its viscoelastic properties, HA can affect cellular processes that alter the extracellular and cellular environments. When it comes to treating periodontal illnesses, the material's viscoelastic qualities may help to block the entry of germs and viruses [17].

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**3. Bacteriostatic qualities**: Regenerative surgery treatment outcomes may be enhanced by lowering the bacterial load at the wound site. Research has demonstrated that by lowering the risk of infection following surgery, HA has bacteriostatic effects and inhibits the growth of different bacterial strains [18].

**4. Biocompatibility and non-antigenicity**: Because HA is biocompatible, it promotes bone healing and regeneration as well as the repair and regeneration of surgical wounds and periodontal tissue. Furthermore, it is fully biodegradable and promotes the proliferation of fibroblasts, chondrocytes, and mesenchymal stem cells [19].When HA is administered, granulomatous and inflammatory reactions occur gradually and persistently. Additionally, applying HA to human immune cells causes a low-grade inflammatory response that activates T cells [20].

**5. Anti-inflammatory and antioxidant activity**: It's thought that high molecular weight forms of HA can drain prostaglandins and metalloproteinases and trigger different proinflammatory reactions by acting as a scavenger and protecting against the impacts of reactive oxygen species [21].

**6. Anti-oedematous**: The osmotic activity of HA may also have an impact on its anti-oedematous properties. It may be used in conjunction with mechanical therapy because of its ability to accelerate tissue healing [22].

**7. Antioxidant**: Hyaluronan, in a rather paradoxical way, may control the inflammatory response by scavenging reactive oxygen species (ROS) and functioning as an antioxidant. Hyaluronan may thus aid in stabilising the matrix of granulation tissue [23].

**Formulations of HA**: In the past few years, HA formulations have been created for topical use as an adjuvant treatment for periodontal and gingival illnesses, as well as for the regeneration of tissue following implant surgery and tooth extraction.

**A. HA-based powder gel**: HA-based powder gel (200 microgramme) is a preparation made by combining β-tricalcium phosphate microspheres, which function as an efficient carrier for implantation in the host bone, with porous spherical particles of recombinant human bone morphogenetic protein-2 (rhBMP-2). By absorbing the blood and other fluids produced at the site of the defect, the powder gel makes it easier for rhBMP-2 to be loaded at the location of the bone defect [24].

**B. HA spray**: HA has been utilised as a spray in the early postoperative phase after extractions, and it seems to be useful in reducing trismus and oedema. Patient satisfaction with HA spray (0.01%) was higher than that of gel (0.2%), according to Koray M et al. [25]. This may be because HA spray is easier to apply. According to Ibraheem W et al., HA spray has positive benefits on oedema and trismus management in patients' postoperative comfort after impacted third molar surgery [26]. It also promotes the healing of extraction sites.

**C. HA gel**: Applying HA gel topically aids in the healing and repair of tissue. Romeo U and colleagues' investigation demonstrated that applying HA gel to implants with peri-implantitis and the surrounding area may help reduce inflammation and IL-1 β levels in the crevicular fluid. Additionally, following laser surgery, it can encourage quicker secondary intention healing [27]. Topical administration of a HA gel in the peri-implant pocket and surrounding implants with peri-implantitis has been shown by Albrektsson T et al. to decrease IL-1 levels in crevicular fluid and inflammation [28]. After extraction, a 0.8% HA gel formulation was injected into the sockets. The VAS values showed that the groups receiving HA treatment had much less pain [29].

**D. HA mouthwash**: During the post-surgical healing phase, when topical preparation administration may be uncomfortable, mouthwashes might be another convenient option for patients. According to a clinical research, there was a decreased incidence of post-surgical oedema in individuals who received mouthwash containing 0.12% HA and chlorhexidine (CHX). Furthermore, there was a noticeable decrease in bleeding at the surgery site and plaque with HA mouthwash. Likewise, HA mouthwash had a favourable effect on surgical site wound healing [30].

## III. APPLICATIONS IN THE DENTISTRY:

Because of its biocompatibility, biodegradability, and nonimmunogenicity, as well as its involvement in a number of biological processes linked to morphogenesis and tissue healing, HA is essential for bone repair because it promotes the migration, adhesion, and proliferation of undifferentiated mesenchymal cells, which in turn causes them to differentiate into osteoblastic cells. Its physicochemical characteristics allow it to facilitate osteoclast adherence to the bone surface,

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retain osteoinductive growth factors in the surrounding environment, and speed up the production of new bone and revascularisation. in vitro [31]. According to Mendes RM et al., 1% HA promotes the expression of osteogenic proteins such BMP-2 and osteopontin, which quickens the healing process following the extraction of rats' maxillary first molars [32].

Furthermore, HA has bacteriostatic qualities that lower the risk of infection following surgery, speeds up the healing process, and exhibits anti-inflammatory effect by lowering inflammation. Dental implants' osseointegration may benefit from HA's acceleration of osteogenic cell development, which strengthens the bond between the implant and the bone. By influencing the migration, adhesion, proliferation, and differentiation of cell precursors, HA enhances the interface between the implant and the bone [33].

There was undoubtedly a significant impact when HA was used in periodontology to close black interdental triangles with tiny gel infiltrations that went straight into the gum [34].

## IV. FUNCTION OF HA IN DIFFERENT STAGES OF IMPLANT SURGERY HEALING:

One important process that involves several facets of tissue response is the osseointegration of dental implants. This includes neoangiogenesis, inflammation, osteoinduction, and osteoconduction, and is succeeded by the remodelling stage. After osteotomy creates a cavity in the bone, blood first fills the space and then the blood's constituent cells—red blood cells, platelets, and white blood cells—move towards the site where the implant and bone meet. A thick fibrin clot is produced as a result. The first stage of osseointegration is completed when the temporary matrix forms on this fibrin network. [35]

The woven bone that developed during the initial stage of healing becomes lamellar bone, which is made up of parallel fibres, during osseointegration as it adjusts to the loading forces. Both the osseointegration of dental implants and the repair of bone abnormalities go through comparable phases. Therefore, a variety of variables that promote bone repair also support implant osseointegration [36].

According to reports, HA has bactericidal properties. Combining HA with other antibacterial agents could be advantageous for dental implants. Viscoelastic HA inhibits the entry of germs and even viruses into the tissues [37]. Additional uses of HA in dental implant therapy include coating the implant surface to promote osseointegration, combining HA with bone graft material, applying HA to the surgical site to promote healing, treating peri-implantitis, and stimulating bone growth [38]. Following implant surgery, chlorhexidine HA was used with mouthwash to provide an anti-edema benefit without further antiplaque effect. Additionally, experiments with dehiscence were conducted with HA incorporated in the allograft, and the results were generally comparable to those of traditional treatment. Spray-form HA was also investigated for use in the management of peri-implantitis and implant mucositis[39]. In multiple investigations, HA was combined with bone graft material, with a focus on the maxillary sinus lift surgery. Better bone growth was observed when HA was given together with the bone graft [40].

In dentistry, HA-based solutions have been used to cover dental implants to speed up the osseointegration process, to enhance tissue healing after surgery, as an adjuvant therapy for periodontitis and gingivitis, to repair oral ulcers, and to reconstruct the papilla. Combining HA with growth factors, plasma, and platelet-rich fibrin can enhance both soft tissue healing and mineralised wound healing. In order to rebuild the temporomandibular joints, tooth pulp, enamel, jawbone, and root canal, it also functions as a matrix to enclose signalling chemicals and stem cells. It can also serve as a medicine carrier at the nanoscale [38].

## V. DISCUSSION

Monje A et al. claim that adding HA to implant surfaces can increase their bioactivity, which may make it easier to put early loading prosthetic devices that meet patients' needs [41].

According to Pogrel M and colleagues, HA can be found in unstimulated whole saliva at a concentration of 148–1270 ng per milligramme of protein [42].The main causes of this variance in HA levels are individual food variations, dental hygiene practices, heredity, mouth architecture, health and illness states, and other factors. The proteins known as HA synthases, or HAS1, HAS2, and HAS3, are responsible for the normal production of HA in humans [43]. An estimated 85% of the HA is metabolised in the lymph nodes, with the liver and kidneys eliminating the remaining portion. After

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HA is fully broken down, CO2, NH3, acetate, and lactate are produced. Hepatocytes then further metabolise these materials to produce CO2, H2O, and urea [38].

## VI. CONCLUSION

The many clinical investigations have shown that HA is essential for wound healing, and topical HA treatment is crucial for post-extraction healing. According to several studies, HA has an anti-inflammatory and anti-oedematous effect that lowers pain. It also has the ability to speed the reduction of unpleasant sensation in alveolar osteitis, facilitate the osteoinductive process, and promote socket healing following therapy. Owing to its multimodal effect and physiochemical characteristics, HA has been used in many different contexts. Topical HA administration has the potential to enhance oral tissue wound healing, particularly in the initial days following extractions. As a result, HA may be a useful adjuvant therapy for enhancing the process of wound healing following extraction.

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