Review Article

Hyaluronic acid: Hope or hype in periodontics – A narrative review

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Abstract:

The use of novel and cutting-edge materials has always existed in dentistry. For many years, dentists have considered environmental and behavioral factors that affect disease and treatment response when making patient care decisions. Considering its superior biological qualities, hyaluronic acid (HA) has attracted a lot of attention in a variety of medical domains. Its applications in dentistry have been investigated in periodontology, oral surgery, and even restorative dentistry. In the realm of dentistry, HA has attracted a lot of interest as a prospective treatment with promising results. The optimism around HA's use in dentistry is examined in this research to determine whether it is supported by reliable data or whether it is the result of overstated assertions. This review article objectively assesses the potential advantages and restrictions of HA application in dental practices through a thorough evaluation of the pertinent literature and clinical data. The purpose of this study is to provide a fair evaluation of whether HA represents a beacon of hope or if it is primarily the result of unfounded hype by looking at its efficacy in various dental procedures and therapeutic uses.

Key words:

Hyaluronic acid, hyaluronic acid for gingivitis, hyaluronic acid for periodontitis, periodontal therapy

INTRODUCTION

Hyaluronic acid (HA), a naturally occurring molecule in the human body also known as hyaluronan or hyaluronate, has captured the interest of researchers, medical experts, and the cosmetics industry due to its numerous health-improving properties. HA is extensively utilized in various applications, including skin care, joint therapy, and dentistry. Dental researchers are exploring HA's potential advantages in oral health and treatment methods because of its essential contribution to the extracellular matrix (ECM) and synovial fluid, as well as its role in tissue repair, wound healing, and inflammatory management.[1]

HA has proven to be a useful material for various treatment modalities such as wound and ulcer healing, as an adjunct to scaling and root planing, for treatment of periodontal diseases, etc., to mention a few.

HA is a high-molecular-weight glycosaminoglycan found in synovial fluid, serum, saliva, and gingival crevicular fluid.[1] It also makes up a significant portion of the ground substance of both mineralized and nonmineralized tissues, including the periodontium. It is a major component of the ground substance in both mineralized and non-mineralized tissues, with higher concentrations in soft tissues of the periodontium, such as the gingiva and the periodontal ligament , compared to the hard tissues like alveolar bone and cementum. Some important cells of the human body that play a role in the production of HA in the cell membrane are fibroblasts, chondrocytes, and osteoblasts in the presence of endotoxins. Being a critical part of the ground substance, HA plays a major role in cell proliferation, migration, and maintaining tissue hydrodynamics.[2]

HA has been enthusiastically implemented in dentistry due to its positive characteristics, which include anti-inflammatory, analgesic, and regenerative capabilities. Its potential uses in dental implantology, oral surgery, periodontal therapy, and even oral hygiene products have been researched. The crucial question, therefore, is whether HA in dentistry represents legitimate hope or is merely marketing hype.

To fully capitalize on HA's potential in the field of dentistry, a fair and evidence-based assessment will enable more responsible decision-making and the identification of areas requiring further research.

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HISTORY OF HYALURONIC ACID

Meyer *et al*. discovered HA in 1934. A team of researchers at Columbia University in New York, led by John Palmer, identified a molecule from a cow's eye's vitreous fluid. They proposed the acronym HA since it included two sugar molecules, the first of which was uronic acid, and came from the Greek word hyalos, which denotes "glass." At the time, the researchers had no idea that the substance they had discovered would end up being one of the most intriguing and useful natural macromolecules.[3]

THE ESSENCE OF HYALURONIC ACID: CHEMICAL STRUCTURE, NATURE, AND SYNTHESIS OF HYALURONIC ACID

HA is a naturally occurring glycosaminoglycan of high-molecular-weight 4000–20,000,000 daltons that is nonsulfated in nature. The chemical structure of HA consists of repeating units of polyanionic disaccharides. These disaccharide units of N-acetylglucosamine and glucuronic acid are connected through a sequence of β1-3 and β1-4 bonds that extend up to the length of 2–25 μm.[4]

HA turnover primarily occurs through metabolic breakdown within densely organized tissue that lack lympathatic drainage. The HA content in tissues changes through two mechanism: local metabolism or lymphatic outflow into the bloodstream.

About 20%–30% of HA turnover in the skin and joints is caused by local metabolism, with the remaining percentage being eliminated by lymphatic routes. Upon entering the bloodstream, the liver removes 85%–90% of it. Only 1% to 2% of the kidneys' excretion is found in urine.[5] Regardless of its mode of removal, HA has a half-life in tissues that span from a few hours to 2 or 3 days. With a half-life ranging from days to weeks, HA is mostly restricted to the tiny intracellular spaces found in skin tissue. The prevailing consensus is that the destruction of it throughout the vertebrate body is mostly caused by the hyal enzymes, also known as hyaluronidases. Reactive oxygen species (ROS) or enzymatic degradation are the two methods by which HA can be degraded. Even while both processes happen at the same time, it is still unclear how much of each they contribute.[6,7]

D-glucuronic acid and N-acetyl-D-glucosamine repeating units make up the precise molecular structure of HA. The monosaccharides are joined by alternating 1,3- and 1,4-glycosidic linkages in the polysaccharide's main structure, which is a linear, unbranched chain. There are hydrophobic faces in the secondary framework of HA, which are made up of the axial hydrogen atoms of around eight carbon–hydrogen groups on the molecule's alternate sides. Such hydrophobic areas energetically favor the development of sheet tertiary structures that resemble meshwork because of molecular aggregation. Hydrogen bonds between molecules help to stabilize the tertiary structure.[6] Large molecules can congregate thanks to the hydrophobic nature and hydrogen bonding contacts, along with the opposing electrostatic repulsion to create webs (matrices) of molecules. HA has been widely used in periodontal treatments because of its acid group, which allows for chemical modifications such as esterification and peptide coupling reactions. This is especially true in drug delivery systems for targeted therapies that aim to reduce inflammation and promote tissue regeneration.[8]

HYALURONIC ACID: A KEY INGREDIENT IN PERIODONTAL TREATMENT

Although HA has had a significant impact on most domains in the field of medicine, it also requires further input from the field of dentistry. In the field of dentistry, it was not until 1997 that Vangelistic *et al.* and Pagnacco *et al.* used HA for the first time.[7] HA is an important component of the ground substance, and its role in growth factor interactions, the regulation of osmotic pressure, and tissue lubrication are just a few of the structural and physiological roles that hyaluronan plays in tissues. These roles all contribute to the structural and homeostatic integrity of tissues.

HA has an array of fascinating applications in dentistry [Figure 1] due to its qualities, which include hydration, biocompatibility, anti-inflammatory effects, tissue regeneration, analgesic capabilities, and biodegradability.[9] Although these characteristics provide promises for improving dental care and treatment outcomes, it is important to approach the subject critically and base judgments on solid scientific data.

EXPLORING THE LIMITLESS POSSIBILITIES: INTEGRATING HYALURONIC ACID IN ROUTINE DENTAL PRACTICE

Finding novel solutions that improve patient care and outcomes is a never-ending effort in the dynamic field of modern dentistry. The use of HA in everyday clinical settings is one such breakthrough that has attracted a lot of attention and shows great promise. With its exceptional qualities and a wide variety of uses, HA presents numerous chances to raise the level of dental care offered to patients.

HA is proposed as a potential biomaterial with notable regenerative benefits and unique properties, including biological and physical characteristics, at a potentially lower cost. HA has been suggested as a viable dental material for promoting healing in periodontal wounds, treating gum recession, regenerating intrabony periodontal defects, yielding positive outcomes in raising the clinical attachment level, and decreasing probing depth. HA's effectiveness can be linked to its capacity to boost the health and growth of periodontal ligament fibroblasts, encourage the development of osteoblasts, and adjust the body's inflammatory reactions. HA enables cellular migration, adhesion, and proliferation by binding to cell surface receptors like CD44, and it also participates in the formation of new blood vessels, a process known as angiogenesis. HA also plays a role in the organization of the ECM, leading to elevated collagen production and the formation of new bone, thereby aiding in the regeneration of periodontal tissues.[10,11]

Efficacy and safety of hyaluronic acid in scaling root planing

One of the most routinely done procedures in dentistry that plays a crucial role in maintaining the health of periodontium is scaling and root planing (SRP). SRP improves periodontal parameters by

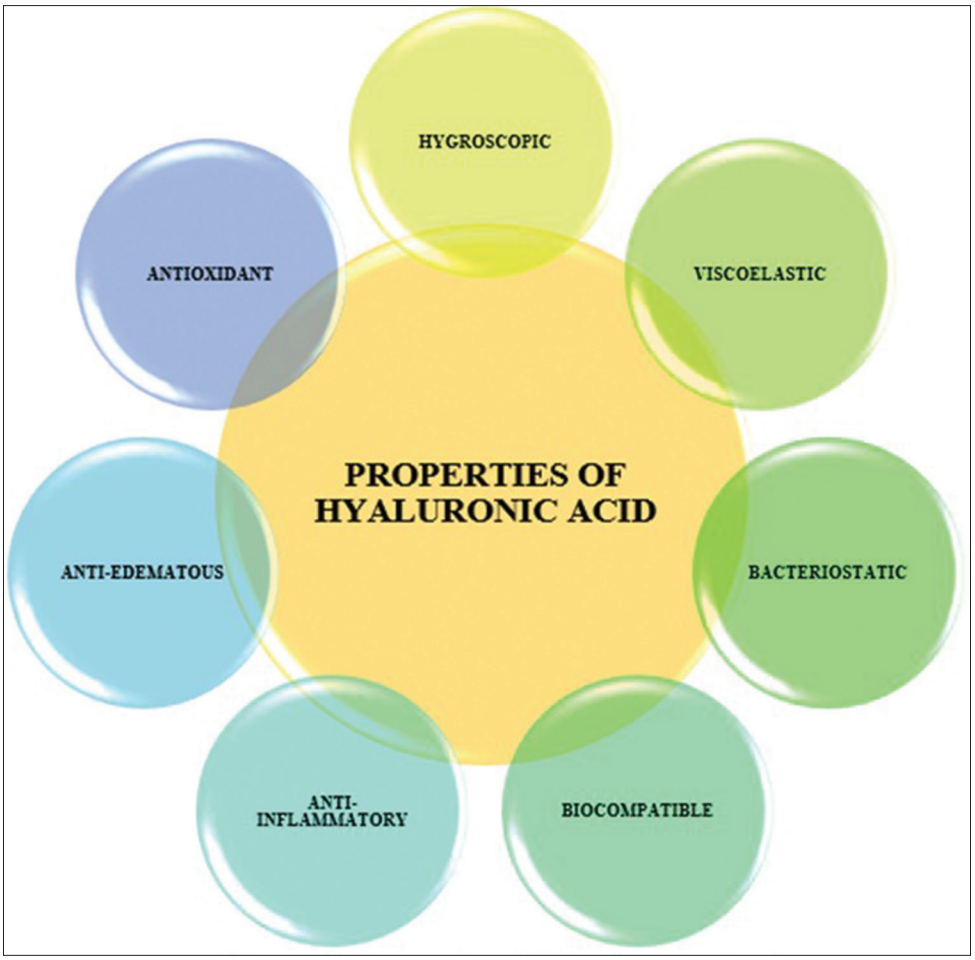

Figure 1: Properties of hyaluronic acid

reducing the overall number of bacteria in the periodontal pocket and changing the microbiota to make it less harmful. In 1993, Giannobile *et al*.[12] demonstrated that gingival tissue contained HA. In a clinical experiment, Nguyen *et al*. added 0.2% HA as an adjunct to SRP for periodontitis patients.[13] In clinical trials carried out in 2014, Rajan *et al*.[14] used HA in 33 individuals with chronic periodontitis. Participants in the test group were tested using a combination of HA + SRP. They concluded that there was a higher reduction in bleeding during probing and probing pocket depth in the test group. This might be explained by the fact that after SRP, the HA content in the periodontal pockets lasts for at least 1-several days[9] encouraging tissue regeneration and repair as HA has been shown to influence fibroblast morphology and increases collagen production,[15] encouraging the reattachment of the gingiva to the root surfaces.[14]

It is crucial to remember that HA should not be considered a replacement for SRP, which is the recommended primary treatment. SRP is an essential nonsurgical technique for controlling periodontal disease and eliminating plaque and calculus supra- and subgingivally. If combined with SRP, HA is intended to supplement the usual treatment and maybe improve its results.

Periodontal regeneration

Another simple yet effective treatment modality that is recommended to patients who are a part of the periodontal maintenance phase is the administration of local drug delivery (LDD) in periodontal pockets that persist even after SRP. Fibroblasts, a type of periodontal ligament cell, play a significant role in the healing of periodontal wounds due to their capacity to transform into bone cells and cementoblasts. Activation of signaling molecules such as Akt, ERK1/2, and p38 by HA significantly impacts its behavior. Studies conducted in a laboratory setting show that HA enhances cell growth, movement, and the expression of key genes such as COL3A1 and TGFB3, which are necessary for wound healing without scarring. Furthermore, HA increases the production of genes that code for growth factors crucial for repair, including platelet derived growth factor subunit B (PDGFB), fibroblast growth factor 2, and epidermal growth factor, and facilitates the remodeling of the ECM through the stimulation of matrix metalloproteinase (MMP) genes, such as MMP1 and MMP8.[16] Numerous LDD methods have been established to prevent the negative consequences of systemic antibiotic therapy. HA has been gaining momentum as an LDD as it seems to be more effective against most periopathogens while having little to no effect systemically.[15] It is being considered an adjuvant to both nonsurgical and surgical therapy in periodontology because of its anti-inflammatory, antimicrobial, and regenerative capabilities.[14] However, the efficacy of HA is only seen after the removal of dental biofilm and SRP. HA alone proves to have little to no effect on the health of periodontium and periodontal

pockets. The notion was tested in studies by Shah *et al*.[17] in 2016 and Chauhan *et al*. in 2013[18] to determine the effectiveness of HA as an LDD following nonsurgical periodontal therapy. In their study, they concluded that there was an increased relative clinical attachment level and decreased probing pocket depth. HA remains in the periodontal pocket for a long time when used as a drug delivery method. This facilitates the therapeutic agent's continued release for around 1-several days, according to the study conducted by Fraser *et al*., in 1997,[5] ensuring that it is exposed to the damaged area for an extended period and maximizing its therapeutic effects.[19] Although studies highlight the regenerative capacity of HA, further studies, especially histological studies, are needed to conclude the same.

Pioneering solutions for treating black triangles

Considering HA stimulates neovascularization, treatment with injectable HA gel in various doses improved papillary regeneration. It exhibits growth factor interaction, controls osmotic pressure, and improves tissue lubrication, all of which contribute to the preservation of the architectural and homeostatic integrity of tissues and have a positive impact on the missing interdental papilla. HA, carboxyl groups, are fully ionized at extracellular pH. It greatly affects the distribution and flow of water due to its nonideal and disproportionately high osmotic activity concerning its molecular weight. As a result, HA is essential to preserving water homeostasis.[8] This property thus helps HA to attract water and swell up and create volume for structural integrity.

The nonsurgical technique to restore the interdental papilla by administering 0.2% HA is a minimally invasive method that significantly alters the volume of the interdental papilla along with decreasing the postoperative discomfort in the patient. This has proven to be a huge advantage that adds to the already existing fanfare around HA.[17,18,20,21] Granted, HA injections improve the appearance of periodontal health and enhance the treatment regimen, but further studies to overcome current challenges are need of the hour.

Revolutionizing gingival recession treatment

Gingival recession is a frequently encountered clinical finding and occurs in more than 90% of individuals with proper oral hygiene. The most common reasons why these patients seek treatment are buccal exposure of roots with esthetic issues and dentinal hypersensitivity. Studies on animals and *in vitro* have shown that HA considerably elevates granulation tissue's tensile strength. It has recently been demonstrated to increase ligament cell viability. Single Miller Class I gingival recession sites can be treated with a variety of surgical root covering procedures accompanied by the application of HA therapy predictably and securely. HA promotes cell migration and differentiation during the development of new tissues and their repair. Nevertheless, it is important to remember that the properties of HA that are held in such high regard for the treatment of recession are mere additive properties to the existing surgical techniques.[22,23]

Forging strong bonds and osseointegration in implant dentistry

The impact of HA on osseointegration and soft-tissue integration in implantology is an exciting possibility. The long-term success of implant treatments might be improved using HA-coated implant surfaces or HA as a component of bone graft materials.

Mesenchymal stromal cells and preosteoblast cells, which play a vital role in osteointegration, are modulated by hyaluronan, which directs them toward self-renewal and osteogenic differentiation, respectively. It is hypothesized that HA, which is known to have an osteoinductive effect during the regeneration of bony defects, would also have a positive impact on osseointegration, a specialized process that repairs bone.[24] HA controls osteogenesis-related cell behaviors through both indirect mechanisms, such as its physical and chemical properties, and direct interactions by binding to cell surface receptors. The CD44 receptor, a key component, influences osteogenic cell activities when HA binds to it, whereas receptor for HA-mediated motility (RHAMM) primarily regulates cell mobility. The biological functions of HA in bone regeneration are significantly impacted by its molecular weight. High-molecular-weight HA (900–2300 kDa) causes an increase in the expression of osteogenic gene markers, such as RUNX-2, ALP, and OCN, whereas low-molecular-weight HA (60 kDa) promotes cell proliferation and differentiation.[25,26] HA's diverse functions in microenvironment regulation, cellular signaling, and ECM composition highlight its significance in bone biology. The incorporation of HA into clinical approaches may open the door for improved therapies and interventions in bone regeneration and repair as research into the intricacies of HA's impact on bone tissue homeostasis progresses. Although there has been a lot of development, more investigation and clinical studies are necessary to fully comprehend the ideal HA dosages, administration strategies, and long-term effects on osseointegration.[24]

Managing oral wounds and ulcers

A somewhat typical condition involving the oral mucosa is oral ulcers. Mouth ulcers are frequent and typically brought on by trauma from things such as poorly fitting dentures, broken teeth or fillings, bites (most commonly at the level of the cheek), or burns from eating food that is too hot. The HA-based gel proved effective for healing ulcers in the oral cavity. In addition, it has been established to be superior in drastically reducing erythema, exudation, and ulcer size. High-molecular-weight HA, with a molecular weight exceeding 500 kDa, displays both anti-angiogenic and immunosuppressive characteristics, and its hydrophilic structure facilitates cell migration, a crucial aspect of the wound healing process. HA interacts with cells by binding to specific receptors, including CD44, RHAMM, and ICAM-1. CD44 promotes cell migration, proliferation, and HA breakdown; in contrast, RHAMM is linked to the movement of mobile cells, and ICAM-1 affects leukocyte integrin binding. Proteins that bind to HA (hyaladherins) facilitate the assembly of the ECM and cell interactions. HA oligosaccharides stimulate the formation of new blood vessels, thereby facilitating tissue regeneration. HA has been found to exert anti-inflammatory properties through the inhibition of prostaglandins, metalloproteinases, and ROS, as well as enhancing fibrin clot formation.[27-29] In 2011 and 2006, Kapoor *et al*. and Nolan *et al*. experimented with the use of HA for patients with recurring aphthous ulcers. When scientists compared the usage of HA with a placebo group,

they discovered that patients who received HA gel for ulcers recovered more quickly and felt less pain. They claimed that the amount of time needed for healing greatly decreased. The ability of HA to hold onto moisture (hygroscopic nature) may generate the ideal conditions for wound healing, which helps speed up the healing process. Its use could make patients feel more comfortable by easing their discomfort, pain, and sensitivity.[30]

Fibroblasts are essential to produce ECM components in oral wound repair. HA stimulates the growth of new blood vessels and fibroblasts. Hyaluronan synthesis by endothelial cells (ECs) is stimulated by HA during periodontal wound healing, which amplifies the inflammatory response. Because of its advantageous benefits, HA is widely used in periodontal therapy. Studies conducted on animals, as well as *in vitro*, have demonstrated that HA speeds up the healing process.[31,32]

It is commonly known that HA promotes angiogenesis. According to an *in vitro* study, HA activates ECs' HA receptors to promote angiogenesis. Ten days following HA treatment, a prior histological investigation found a noteworthy rise in newly created blood vessels in human oral lesions.[33] Furthermore, Pilloni *et al*. discovered that the treated and control groups' gingival epithelial cells exhibited comparable cell proliferation when subjected to an immunohistochemical study of Ki-67 expression. Histological examination also showed that there were no indications of inflammatory infiltration and that the gingival structure was unaffected by the HA therapy.[34]

Hyaluronic acid in tissue engineering

The utilization of HA and its derivatives in scaffold construction for tissue engineering (TE) is widespread because of its improved biocompatibility, regulated cross-linking, and appropriate porosity for cell encapsulation, differentiation, and proliferation. Scaffolds based on HA have been thoroughly investigated, especially in the field of cartilage TE. When creating TE scaffolds that work, factors such as biocompatibility, biodegradability, cytocompatibility (which promotes cell adhesion, growth, and function retention), and appropriate mechanical qualities for the implantation site must all be carefully considered. For the best possible cell infiltration and vascularization, these scaffolds must strike a compromise between mechanical strength and porosity while maintaining repeatability. HA has been thoroughly investigated for the synthesis of bioscaffolds in TE because it satisfies most of these requirements.[35]

FUTURE AVENUES FOR THE APPLICATION OF HYALURONIC ACID

HA has tremendous promise in periodontal therapy, implantology, wound healing, orthodontics, caries prevention, and cosmetic surgeries. In future, it may be used as a stable drug delivery system, support tissue regeneration, increase implant stability, and encourage soft-tissue repair in conjugation with certain growth factors. Its potential for bone regeneration and esthetic dentistry further demonstrates its applicability in dental treatment.[36]

NAVIGATING NEW FRONTIERS: CHALLENGES IN HARNESSING HYALURONIC ACID FOR DENTAL APPLICATIONS

Limited clinical evidence

A comparison of HA treatments to others, such as guided tissue regeneration, enamel matrix derivative, and growth factors,[37-40] shows its biocompatibility, anti-inflammatory effects, and user convenience. Despite being cost-effective and versatile, HA's quick breakdown in the mouth severely restricts its effectiveness in comparison to more advanced treatment methods. Currently, despite increasing interest in its application in dentistry, insufficient robust clinical data exists to fully substantiate its effectiveness and reliability across a range of dental treatments. Establishing optimal dosages, administration methods, and treatment plans requires rigorous clinical trials and long-term studies, thereby ensuring consistent and reliable results that fully leverage HA's benefits [Table 1].

Standardization of formulations

There are many different formulations and molecular weights of HA, and each one may have an impact on how effective it is as a treatment. Standardization of HA products is essential to provide consistent results and enable comparisons between various types of research. The main conclusions about HA's efficacy in dentistry are difficult to arrive at because there are not any standardized formulations. The complexity of regulatory approval for HA products can be clarified by examining in detail specific instances of classification and approval procedures in both the US and European markets. Regulatory bodies classify medical devices to guarantee safety and efficacy, with varying methodologies employed by each. In Europe, medical devices are grouped into four categories (I, IIa, IIb, and III) based on their level of risk, with a differing system being employed by the US Food and Drug Administration (FDA), which classifies devices into three categories (I, II, and III). Most medical devices based on HA, like those employed in viscosupplementation for osteoarthritis, are classified as high-risk devices (Class III in the US, Class IIb, or III in the European union (EU)), necessitating rigorous assessment. Viscosupplementation therapy, which involves intra-articular HA injections for managing osteoarthritis pain, has been classified as a Class III medical device by the FDA for more than 20 years. Products like Monovisc and Supartz FX show the high level of safety and effectiveness that these treatments must adhere to. These products, including HA-based wound dressings, dermal fillers, and ophthalmic solutions, undergo thorough evaluations according to their specific uses. Differences in regulatory frameworks give rise to challenges. Within the EU, obtaining approval under the medical device regulation places significant emphasis on clinical safety, as opposed to the US, where Class III devices frequently necessitate premarket approval, a process involving comprehensive clinical trials and substantial expenses. Seprafilm, an anti-adhesion HA product, was taken off the US market because of allergic reactions, which illustrates the effects of regulatory actions on product availability. These barriers affect the way healthcare professionals work by influencing the availability, cost, and trustworthiness of products. Further examination of these regulatory environments offers significant insights into the worldwide acceptance and refinement of HA-based treatments.[41]

Table 1: Comparison of hyaluronic acid with other treatment modalities

Treatment modality	Advantages	Disadvantages	Comparison with HA
GTR	Effective in promoting periodontal regeneration provides physical barriers for selective cell population	Longer procedural time, risk of membrane exposure, postsurgical complication	HA is easier to use, affordable, avoid complications like membrane exposure, less pronounced results
EMD	Stimulates cementum formation and periodontal ligament attachment, proven effectiveness in intrabony defects	Expensive, potential for allergic reactions, requires advanced surgical techniques	HA is safe and less technique-sensitive but may not match EMD's efficacy in regenerative applications
Synthetic growth factors (e.g.: PDGF, FGF)	Potent stimulation of cell proliferation, effective in large defect repair	Requires precise dosing, high cost, risk of adverse effects	HA has fewer side effects, provides a gradual regenerative outcome
Collagen scaffolds	Provides structural support for cell attachment and growth; bioresorbable and widely biocompatible	May lack intrinsic bioactivity; efficacy depends on combination with other growth factors or bioactive agents	HA is more bioactive, directly promotes cellular response

GTR – Guided tissue regeneration; EMD – Enamel matrix derivatives; HA – Hyaluronic acid; FGF – Fibroblast growth factors; PDGF – Platelet-derived growth factors

Durability and biodegradability

Since HA is known to be biodegradable, questions have been raised concerning the exact number of days it will last when used in conjugation with dental applications. The hurdle is creating HA-based materials that outlast long enough to support the intended healing processes while maintaining their structural integrity and therapeutic qualities.

Local delivery methods

The efficacy of HA in dentistry depends on its effective and regulated local distribution to the target region within the oral cavity. It is challenging in terms of technique to create appropriate delivery systems, such as gels, films, or scaffolds, that guarantee prolonged release and good adhesion to oral tissues.

Immunogenic reactions

Although HA is typically thought of as biocompatible, there is a chance of immunogenic reactions, particularly when used at larger concentrations or over longer periods. To fully comprehend the immunological reactions to HA in dental applications and to minimize any negative effects, more study is required.

Regulatory approval and guidelines

The regulatory approval process for HA-based dental products can be complex and time-consuming. Developing clear guidelines and standards for the use of HA in dentistry, along with navigating the regulatory landscape, presents a challenge that requires collaboration between researchers, clinicians, and regulatory agencies.

Patient education and awareness

It is vital to familiarize and enlighten patients before introducing a novel therapy strategy like HA in dentistry. It may be necessary to try to adequately communicate the benefits, risks, and prospective outcomes to gain the trust and acceptance of patients for HA-based therapy.

SUMMARY AND CONCLUSION

A vital query that arises from this is, "Is HA a genuine hope or simply marketing hype??". Yes! HA demonstrates a wide range of assets, from being an additive to daily routine to being an important biomaterial that aids in major periodontal surgeries. Over the coming years, we will obtain further information on the use of HA and its overall efficacy in the field of dentistry. This group effort will lead to the discovery of novel ways for the use of HA, which will be extremely beneficial.

Aside from the expectations, HA has set in the minds of clinicians and researchers, the prospect is that physicians will, in the next few years, be expected to critically analyze the true nature of HA. Researchers are expected to compile all the potential negative effects that HA could have when used intraorally. HA can completely transform a variety of therapy approaches, from tissue regeneration to wound healing. To successfully integrate it into conventional dentistry practice, it is necessary to solve the impending issues with clinical evidence, formulation standardization, local delivery modalities, immunogenic reactions, and regulatory concerns. To overcome these obstacles and fully use HA's advantages in improving dental care, collaboration among researchers, doctors, and regulatory agencies is vital.

How the systematic exploration of HA and its variants will transform diagnostic and clinical practices remains to be seen, but tempered by the challenges discussed here, HA bolsters hope for sustained and meaningful improvements in the diagnosis, prognosis, and treatment of individual patients.

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Conflicts of interest

There are no conflicts of interest.

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