Hyaluronic Acid in Periodontal Regeneration: Evidence, Applications, And Future Prospects

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***Abstract*—The naturally occurring glycosaminoglycan hyaluronic acid (HA) is crucial for lubrication, wound healing and tissue hydration. Its unique physicochemical and biological characteristics have garnered growing interest in periodontal treatment, particularly in addressing the complex challenge of restoring the damaged periodontal structure. HA functions as an efficient scaffold that promotes cell migration, proliferation, and the development of new blood vessels because of its viscoelastic characteristics. Additionally, its anti-inflammatory, bacteriostatic, and tissue-repairing capabilities position it as a valuable adjunct in both non-surgical and regenerative approaches within periodontics. This review explores the foundational biology, functional mechanisms, and therapeutic applications of HA in periodontal care, emphasizing current research findings and potential future developments in regenerative strategies.**

***Index Terms*—Hyaluronic acid, periodontal regeneration, guided tissue regeneration, wound healing, peri-implant therapy**

I. INTRODUCTION

Rebuilding the periodontium's damaged tissues and functions is the aim of periodontal regeneration. While traditional approaches like mechanical cleaning and surgical procedures remain foundational, the integration of biomaterials - such as bone substitutes, barrier membranes, and biological agentshas shown promise in improving healing outcomes[1]. Due to its many biological roles, such as encouraging tissue healing, boosting the development of new blood vessels, and supporting cell growth, hyaluronic acid (HA) has become a major factor.[2]. HA was introduced by Meyer and Palmer in the year 1934, a naturally occurring glycosaminoglycan consisting of repeating units of D-glucuronic acid and N-acetyl-D-glucosamine, connected by alternating β1–3 and β1–4 bonds. It is widely distributed throughout vertebrate tissues in the extracellular matrix of synovial fluid, connective tissuesand the periodontal ligament[3]. HA contributes to tissue hydration, lubrication, structural supportand cellular communication via receptors like CD44 and RHAMM. Its abundance in periodontal structures has led to extensive research into its clinical applications, ranging from non-surgical treatments and regenerative procedures to soft tissue reconstruction and peri-implant therapies[4]. Current studies and reviews continue to highlight HA's compatibility with biological tissues and its potential to enhance regenerative outcomes in periodontal care.

II. ORIGIN AND METABOLISM OF HA

The hyaluronic acid (HA) emergence dates back to 1880 where Portes from the vitreous body of the eye, a unique mucin distinct from other mucoids, and termed it "hyalomucine." In 1934, Karl Meyer and John Palmer at Columbia University separated a polysaccharide from bovine vitreous humor that was

made up of an amino sugar and uronic acid. They called this substance "hyaluronic acid," which is formed from the words "hyaloid" (glass-like) and "uronic acid."[1]

Initially extracted from animal tissues, HA production advanced to bacterial fermentation, particularly using Streptococcus species, to yield high molecular weight HA with minimal contamination. Purification typically involves centrifugation, ultrafiltration, and size-exclusion chromatography, producing highly pure biomedical-grade HA[2]

The HA turnover in tissues happens through local metabolism or lymphatic drainage into the bloodstream. About 20–30% of HA in skin and joints is metabolized locally, while the remainder is cleared via lymphatic pathways[3]. Once in circulation, around 85–90% is degraded in the liver, and remaining is filtered by the kidneys of about 10%, with only 1–2% excreted in urine[4]. The half-life of HA in tissue typically occurs for about 12 hours to 2–3 days, depending on the site and metabolic activity[5].

III. CHEMISTRY AND STRUCTURE OF HYALURONIC ACID

Repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine make up hyaluronic acid (HA), an unbranched linear polysaccharide that occurs naturally.(Figure 1) These monosaccharides form a continuous polymer chain with a high molecular weight and exceptional physicochemical stability when they are alternatively joined by β-1,3 and β-1,4 glycosidic linkages[3].

Hydrophobic faces with axial hydrogen atoms of about eight carbon–hydrogen (C–H) groups arranged on alternating sides of the molecule are present in HA's secondary structure. Through molecule aggregation, these hydrophobic patches encourage the creation of a meshwork-like β-sheet tertiary structure, which is further maintained by intermolecular hydrogen bonding. Many HA chains can aggregate into three-dimensional molecular networks (matrices) because to a mix of hydrophobic and hydrogen-bonding interactions that are counterbalanced by electrostatic repulsion from negatively charged carboxylate groups[6].

The presence of carboxylate groups also imparts a negative charge to the HA molecule, enabling it to form hydrophilic salts with a high capacity for binding and retaining water. This property confers HA with exceptional viscoelasticity, hygroscopicity, and biocompatibility, act as a shock absorber, lubricant, space filler, and regulator of tissue hydration and water balance. Collectively, these molecular and structural features form the biochemical basis for HA's diverse biological roles in tissue protection, regeneration, and wound healing[3].

IV. PROPERTIES OF HA

The general properties of Hyaluronic acid (HA) are (Figure 2)

Hygroscopic Nature:

One of the most hygroscopic substances found in nature is hyaluronic acid (HA). Adjacent carboxyl and N-acetyl groups establish hydrogen bonds when integrated into an aqueous environment, allowing HA to retain water and preserve its conformational stiffness. Amazingly, up to six liters of water can be bound by one gram of HA. Because of this characteristic, it can serve as a physical background substance that fills spaces, lubricates, absorbs shock, and excludes proteins. Its potent water-binding ability aids in tissue hydration and protection during wound healing in periodontal applications[7].

Viscoelastic Properties:

HA exhibits distinct viscoelastic characteristics that play a critical role in periodontal regenerative procedures by maintaining space, protecting surfaces, and facilitating cellular functions within the extracellular matrix. The viscoelastic nature influences the surrounding microenvironment by modulating cell adhesion and migration. Moreover, this property may help slow the penetration of viruses and bacteria, which is particularly beneficial in managing periodontal infections and promoting stable wound healing[7].

Bacteriostatic Effect:

Clinical and experimental evidence indicates that reducing bacterial burden at surgical or wound sites enhances the success of regenerative therapy. Medium to low molecular weight HA exhibits a notable

bacteriostatic effect, particularly against Aggregatibacteractinomycetemcomitans Prevotellaoris, and Staphylococcus aureus—microorganisms commonly associated with periodontal and gingival lesions. Application of HA in the form of gels, membranes, or sponges during surgery may reduce bacterial contamination, minimize postoperative infection risk, and promote predictable regeneration[8].

Anti-inflammatory Activity:
HA exerts significant anti-inflammatory effects by acting as an exogenous scavenger for proinflammatory mediators such as prostaglandins, metalloproteinases, and other bioactive molecules. By draining these mediators and neutralizing free radicals, HA helps control local inflammation, reduce tissue destruction, and facilitate an environment conducive to repair[9].

Anti-oedematous Effect:
Because of its non-ideal osmotic pressure, which rises exponentially with concentration, A exhibits a special osmotic buffering capacity. Because of this characteristic, it can control interstitial fluid balance and tissue hydration, which has an anti-oedematous effect. By minimizing edema and improving nutrient diffusion, HA further enhances tissue healing and recovery following periodontal therapy[10].

Antioxidant Function:
By scavenging reactive oxygen species (ROS), HA also acts as an antioxidant, lowering oxidative stress and regulating the inflammatory response. This function stabilizes the granulation tissue matrix and supports orderly tissue regeneration[8].

Non-antigenicity and Biocompatibility:
Because HA is highly biocompatible and non-immunogenic, it can be used in a variety of biomedical applications, such as joint lubrication for arthritis, surgical assistance in ophthalmology, and scaffolding for the regeneration of bone and periodontal tissue. Chemical modifications such as esterification and cross-linking further enhance HA's structural integrity, allowing its use as a biodegradable matrix that supports the proliferation and development of mesenchymal stem cells, fibroblasts, and chondrocytes[7].

V. GENERAL HYALURONIC ACID APPLICATIONS

A versatile biomolecule, hyaluronic acid (HA) plays essential roles in tissue formation and repair. Its ability to form proteoglycan complexes and regulate Cellular processes like migration, adhesion, and proliferation makes it indispensable for both therapeutic and physiological settings. Additionally, HA controls angiogenic and inflammatory reactions, which are critical for efficient tissue regeneration and wound healing[9].

- It promotes healing in periodontal tissues, supports treatment of gingival recession, and facilitates regeneration of intrabony defects by activating fibroblasts and osteoblasts and enhancing extracellular matrix production[11].
- Widely used as a dermal filler, HA provides volume and hydration for soft-tissue augmentation and aesthetic procedures[12].
- Its anti-inflammatory and hydrating properties help minimize scar formation and speed up postoperative recovery[8].
- HA acts as a visco-supplement in joint disorders like osteoarthritis and rheumatoid arthritis, improving lubrication and reducing pain[13].
- Employed as a viscoelastic agent in cataract surgeries and for treating dry eye conditions (xerophthalmia), HA helps protect and hydrate ocular tissues[13].
- Chemically modified HA (through cross-linking or esterification) serves as a scaffold for cell growth and a carrier for targeted medication delivery for topical, nasal, pulmonary, and ocular uses[7].

VI. HYALURONIC ACID AS WOUND HEALING AND PERIODONTAL REGENERATION

Hyaluronic acid (HA) is a natural substance produced in the body by enzymes called hyaluronan synthases (HAS1, HAS2, and HAS3) and broken down by hyaluronidases and reactive oxygen species. Its size affects its function: large HA molecules help maintain moisture, firmness, and tissue structure, while smaller fragments are active in inflammation, healing, and cell communication[11].

VII. MULTIFACETED ROLE IN WOUND HEALING

HA contributes to all major phases of wound healing, making it a versatile and essential component in tissue repair:

- Inflammatory Phase: During the initial phases of recovery, HA integrates into the fibrin clot, providing a hydrated matrix that makes it easier for immune cells like macrophages and polymorphonuclear leukocytes to migrate and adhere. This promotes effective phagocytosis and reduces microbial colonization, particularly in periodontal tissues. HA also causes pro-inflammatory cytokines to be released from fibroblasts, osteoblasts, keratinocytes and hence enhancing initial immune response. As healing progresses, HA modulates inflammation by inhibiting extracellular matrix degradation through serine protease inhibition, helping to preserve tissue architecture[9].
- Granulation and Re-epithelialization: HA supports fibroblast proliferation and extracellular matrix synthesis, contributing to granulation tissue formation. Its degradation by hyaluronidases produces low-molecular-weight fragments that stimulate angiogenesis and promote keratinocyte migration, facilitating re-epithelialization and closure of the wound[11].
- Bone Regeneration Phase: HA increases mesenchymal stem cell recruitment, proliferation, and differentiation—all of which are essential for the development of bones. Like osteopontin and bone morphogenetic protein-2 (BMP-2), it has osteoinductive qualities that promote the growth and development of new bone tissue[8].

VIII. MECHANISMS OF ACTION IN PERIODONTAL REGENERATION:

HA's regenerative potential in periodontal therapy is primarily mediated by its contact with particular cell surface receptors (Figure 3):

- CD44: This receptor promotes cell motility, adhesion, and proliferation. HA stimulates intracellular signaling pathways that support collagen production, angiogenesis, and fibroblast motility when it binds to CD44[9].
- RHAMM (Receptor for HA-Mediated Motility): During wound healing, RHAMM promotes cellular migration and aids in tissue remodeling[11].
- Hyaladherins: These HA-binding proteins help organize the extracellular matrix and stabilize the structural framework of healing tissues[9].

HA also acts as a provisional scaffold within the extracellular matrix, supporting the growth and migration of keratinocytes and other reparative cells. Its hygroscopic nature ensures optimal hydration at the wound site, while its antioxidant properties help neutralize reactive oxygen species, reducing oxidative stress and preserving granulation tissue[8].

IX. CLINICAL APPLICATIONS AND FORMULATIONS

In periodontal and oral wound care, HA is administered topically or via injection in various formulations tailored to specific clinical needs. These include:

- Aqueous gels (typically 0.2%–0.8% concentration)
- Crosslinked fillers for prolonged residence time
- Esterified fibers and membranes for structural support
- Scaffolds combined with graft materials to enhance regenerative outcomes

Products like Gengigel®, a 0.2% high-molecular-weight HA gel, are commonly used in periodontal pockets and surgical sites to promote healing and reduce inflammation. The therapeutic efficacy of HA depends on several formulation parameters, including its concentration, molecular weight, degree of crosslinking, and the nature of the carrier matrix. However, consistent reporting of these variables remains limited in scientific literature, which can affect reproducibility and clinical outcomes[14].

X. CLINICAL APPLICATION IN PERIODONTICS

The following are the clinical applications in periodontics (Figure 4):

1. In addition to root planing and scaling (non-surgical therapy):

The use of topical hyaluronic acid (HA) as an additional treatment in addition to scaling and root planing (SRP) has been the subject of numerous randomized controlled trials (RCTs) and systematic reviews. According to a 2019 systematic review and meta-analysis by Eliezer et al., combining HA with SRP may result in better clinical outcomes, including decreased bleeding on probing (BOP), increases in clinical attachment level (CAL), and decreases in probing pocket depth (PPD). However, the improvements were generally modest, and there was considerable variability in HA formulations and application protocols.

The effects of using 0.2% subgingival HA gel after SRP were evaluated in more recent RCTs, such as one by Nguyen et al. (2021). When compared to SRP alone, their results demonstrated statistically significant decreases in both BOP and PPD. Similar advantages have been documented in other studies2, including those by Rajan et al. (2014) and Al-Shammari et al. (2018), which also observed improvements in clinical indices when HA was used as an adjuvant.

Collectively, the evidence indicates that HA provides consistent additional benefits, particularly in reducing inflammation (as reflected by BOP). However, the extent of improvements in PPD and CAL varies among studies[8].

Clinical Insight: HA enhances soft-tissue healing and reduces bleeding in persistent pockets but should complement or not replace the mechanical therapy.

2.Periodontal Regeneration and Intrabony Defects:

Hyaluronic acid (HA) has been explored in regenerative therapies both as a standalone agent—such as in the form of esterified HA fibers or membranes—and in combination with grafting materials. When HA is utilized as an adjuvant, evidence from case series, smaller randomized controlled trials (e.g., Vanden Bogaerde; Ballini et al.), and systematic reviews shows encouraging increases in radiographic bone regeneration, probing pocket depth (PPD), and clinical attachment level (CAL)1. Robust histology data from human research are still hard to come by, though.

A 2022 systematic review by Rodríguez-Aranda and colleagues, which focused on intrabony defects, also reported positive clinical and radiographic results. Still, variability among studies and the lack of comprehensive histological analysis limit the ability to draw firm conclusions about HA's regenerative potential[11].

Clinical Insight: While HA shows potential to improve regenerative outcomes when paired with standard regenerative materials, more rigorous, histologically substantiated randomized trials are essential to confirm its efficacy.

3. Mucogingival Surgery:

The use of hyaluronic acid (HA) in conjunction with the coronally advanced flap (CAF) procedure for the treatment of Miller Class I gingival recession was assessed in a randomized controlled experiment by Pilloni et al. (2019). According to their results, the group that received HA had a higher chance of attaining full root coverage and a larger decrease in recession depth. Systematic reviews support these outcomes, highlighting modest improvements in soft tissue stability and root coverage when HA is used[7]. Due to HA's known properties—such as enhancing fibroblast proliferation, promoting collagen synthesis, and maintaining tissue hydration—it serves as a promising biological enhancer to improve the consistency of root coverage procedures[9]

Clinical Insight: Incorporating HA in single-tooth mucogingival surgeries may enhance root coverage results, particularly in cases where tissue thickness and healing capacity are critical considerations.

4. Reconstruction of Interdental Papilla (Managing Black Triangles):

Injectable HA fillers have gained traction as a minimally invasive method for restoring lost interdental papillae, commonly referred to as black triangles. Clinical studies and case reports—including those by Pitale et al. (2021), Turgut Çankaya & Tamam (2020), and da Silva et al. (2023)—demonstrate significant improvements in papillary volume and patient satisfaction following repeated micro-injections. The longevity of results varies from several months to a few years, often necessitating periodic maintenance. The degree of interdental bone support and the anatomical nature of the papilla base are two examples of parameters that affect treatment outcome. While systematic reviews show encouraging outcomes, they emphasize the need for randomized controlled trials with standardized evaluation metrics[10]

Clinical Insight: HA injections offer a viable, low-risk solution for aesthetic papillary deficiencies.

Practitioners should inform patients about the potential need for follow-up treatments and the variability in long-term effectiveness.

5. Peri-implant Soft Tissue Management and Peri-implantitis:

Research on HA's role in managing peri-implant conditions remains limited but promising. Preliminary studies suggest that applying HA gel into peri-implant pockets may lead to reduced probing pocket depth (PPD) and improved soft tissue health[6]. Additionally, HA-coated implant surfaces and its inclusion in graft materials for sinus augmentation have shown early signs of enhanced bone regeneration. However, more thorough, long-term clinical trials are required to confirm these advantages because these conclusions are based on small-scale research[15].

Clinical Insight: While HA shows potential in peri-implant therapy, its use should be considered experimental until more conclusive evidence becomes available.

6. Management of Oral Ulcers and Wounds:

Topical HA formulations have demonstrated efficacy in reducing the size, redness, and discomfort associated with recurrent aphthous ulcers and trauma-induced mucosal lesions. These advantages are ascribed to HA's capacity to regulate inflammatory reactions, promote fibroblast activity and preserve a moist healing environment. Clinical trials support its use as a practical and effective treatment option in dental care[8]

Clinical Insight: HA gels are a useful adjunct for managing oral ulcers, offering pain relief and promoting faster healing through non-invasive application.

XI. MECHANISM EXPLAINING CLINICAL EFFECTS

- Anti-inflammatory: Reduces prostaglandins and MMPs; neutralizes free radicals to minimize tissue damage and promote healing[9].
- Healing Support: Creates a hydrated matrix aiding fibroblast migration, angiogenesis (via LMW-HA), and collagen formation[11].
- Antibacterial: Inhibits specific periodontal pathogens at certain molecular weights and concentrations[8].
- Volume Enhancement: Its water-binding and elastic nature helps maintain papilla volume and post-injection stability[12].

XII. SAFETY AND ADVERSE EFFECTS:

Hyaluronic acid (HA), particularly in its purified forms, is widely recognized for its compatibility with biological tissues and low likelihood of triggering immune responses. In periodontal treatments, adverse effects are typically mild and short-lived, such as slight swelling or temporary discomfort—less severe than those observed in other medical applications. Nonetheless, isolated cases of allergic responses have been documented in non-dental uses of HA-based devices. Therefore, dental professionals should be well-informed about the specific characteristics and regulatory approvals of the HA products they utilize. It is important to note that comprehensive long-term safety data on repeated intraoral HA applications remain scarce [13]

XIII. CHALLENGES, DEBATES, AND RESEARCH GAPS

- Diverse HA formulations: Significant variability in molecular weight, concentration, crosslinking methods, and carrier substances complicates the comparison of study outcomes and hinders the development of universal clinical guidelines[14]

- Limited study duration and sample sizes: Many clinical trials are constrained by small participant numbers and short follow-up periods, making it difficult to assess the longevity and sustained efficacy of HA treatments[15]
- Scarcity of histological validation: There is a lack of robust human histological data confirming true periodontal regeneration following HA application[11]
- Unstandardized treatment protocols: The necessity for protocol standardization is highlighted by the lack of agreement regarding the optimal dosage, frequency of administration or timing of surgical interventions. [9]

XIV. FUTURE RESEARCH DIRECTIONS:

1. Uniform data reporting: Clinical studies should consistently document HA characteristics such as molecular weight, crosslinking degree, concentration, formulation type, and detailed application methods[14]
2. Robust randomized controlled trials (RCTs): Large-scale RCTs with histological endpoints are essential, particularly for validating HA's regenerative potential in intrabony defects[11]
3. Long-term studies on papilla augmentation: Research should focus on the durability of papilla reconstruction, optimal maintenance strategies, and comparisons with surgical alternatives[10]
4. Integrative treatment approaches: Investigating the synergistic effects of HA combined with growth factors, platelet-rich fibrin (PRF), stem cells, or bone grafts could enhance both soft and hard tissue regeneration[8]
5. Advanced delivery technologies: The development of slow-release HA systems and functionalized nanocarriers may improve the longevity and effectiveness of HA within periodontal pockets[7]

XV. CONCLUSION

Hyaluronic acid stands out as a promising biomaterial in periodontal therapy, offering biological benefits that support soft tissue healing and regeneration. Evidence from clinical trials and systematic reviews suggests that HA can effectively complement procedures like scaling and root planing (SRP), coronally advanced flaps (CAF), and interdental papilla reconstruction. While early findings on its role in bone regeneration and implant integration are encouraging, they remain preliminary. To fully integrate HA into routine clinical practice, further high-quality, formulation-specific studies with longer period of follow-up and histological confirmation are imperative.

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FIGURES

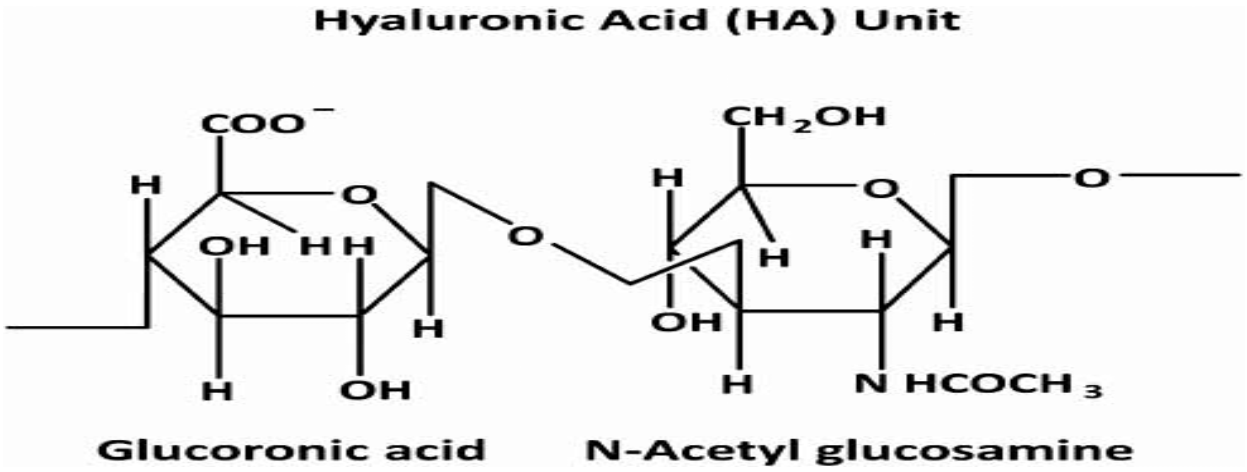


Figure 1: Structure of Hyaluronic Acid Unit

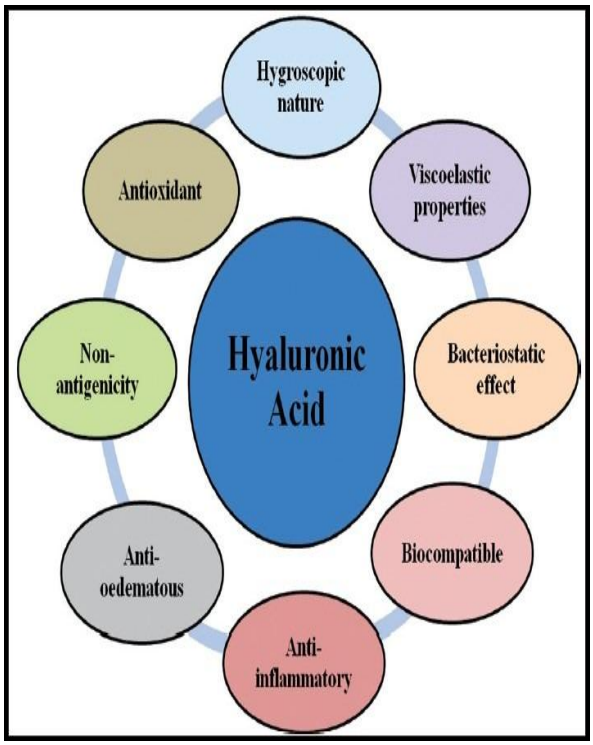
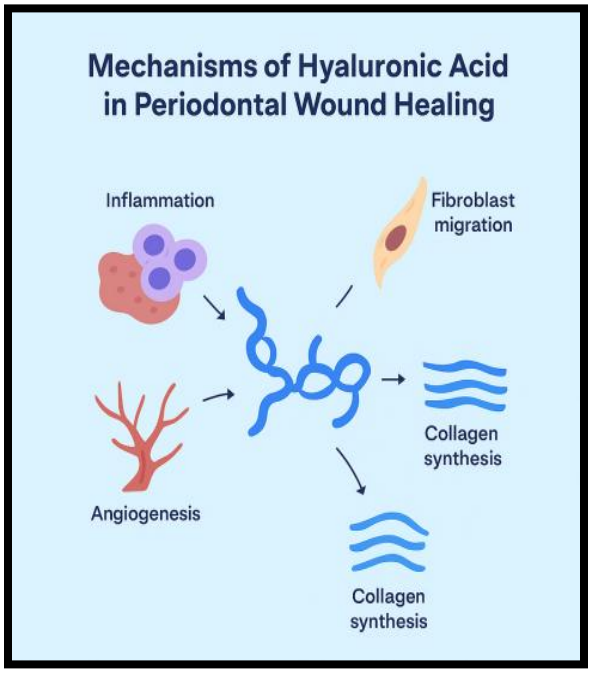
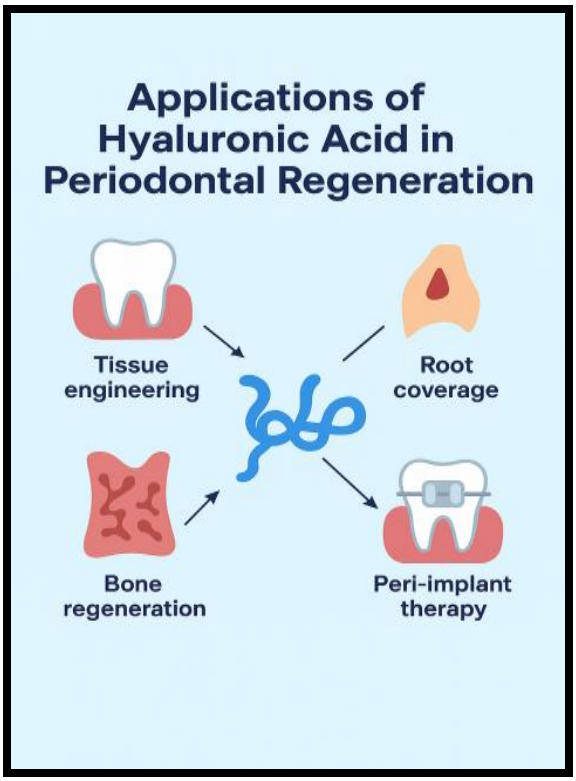


Figure 2: Properties of HA



(Figure 3: Mechanism of HA in wound healing: Hyaluronic acid supports periodontal repair by modulating inflammation, promoting fibroblast migration, enhancing collagen synthesis, and stimulating angiogenesis. These coordinated actions facilitate tissue regeneration and wound stabilization.)



(Figure 4: Clinical application in periodontics: Hyaluronic acid's uses in periodontal regeneration. The four main applications of hyaluronic acid in regenerative periodontics are depicted in this diagram: Peri-implant treatment, bone regeneration, tissue engineering, and root covering.)

Table 1: Summary of major RCT on hyaluronic acid in periodontal therapy

Author (Year)	Study Design & Sample Size	Clinical Indication	HA Formulation / Concentration	Comparison / Control	Main Outcomes	Conclusion
da Silva et al. (2023)[24]	RCT, n = 40	Interdental papilla deficiency	Injectable HA (0.8%) single injection	Saline placebo	↑ papilla height and patient satisfaction	HA significantly improved esthetic parameters
Rodríguez-Aranda et al. (2022)【25】	Systematic review (8 studies)	Intrabony defects (regeneration)	HA membranes/fibers with or without grafts	Conventional GTR	↑ CAL gain and bone fill (0.8–1.2 mm)	HA shows adjunctive regenerative potential
Nguyen et al. (2021)【21】	RCT, n = 60	Chronic periodontitis (non-surgical)	0.2% HA gel (subgingival application)	SRP alone	↓ BOP, ↓ PPD, ↑ CAL at 3 months	Adjunctive HA improved healing and inflammation control

Author (Year)	Study Design & Sample Size	Clinical Indication	HA Formulation / Concentration	Comparison / Control	Main Outcomes	Conclusion
Pini Prato et al. (2020)[26]	RCT, n = 30	Gingival recession	HA gel + CAF	CAF alone	↓ gingival inflammation, ↑ stability	HA enhanced flap adaptation and healing
Pitale et al. (2021)【23】	Prospective RCT, n = 32	Interdental papilla reconstruction	Injectable HA filler (crosslinked, 0.8%)	—	↑ papillary fill index by 1.5 units	Injectable HA effective for papilla augmentation
Turgut Çankaya & Tamam (2020)[27]	Case-control, n = 24	Interdental papilla augmentation	Injectable HA (0.8%)	—	Significant papillary height gain at 6 months	Promising minimally invasive alternative
Pilloni et al. (2019)【22】	RCT, n = 40	Miller Class I recession (CAF)	HA gel (0.2%) applied under CAF	CAF alone	↑ complete root coverage rate (85% vs 60%)	HA improved soft-tissue healing and coverage
Eliezer et al. (2019)【20】	Systematic review & meta-analysis (11 RCTs)	Non-surgical & surgical therapy	0.2–0.8% HA formulations	—	Weighted mean difference: PPD –0.35 mm; CAL +0.36 mm	Adjunctive HA offers modest but consistent benefit
Al-Shammari et al. (2018)[17]	Parallel RCT, n = 50	Chronic periodontitis	0.2% HA topical gel	SRP alone	↓ BOP, ↓ PPD, ↑ CAL	Adjunctive HA enhanced clinical results
Rajendran et al. (2014)	Split-mouth RCT, n = 40	Chronic periodontitis	0.8% HA gel adjunct to SRP	SRP alone	Reduced significantly in BOP and PPD	HA effective as SRP adjunct

Notes for Figure/Table Caption

Table 1. Summarizes the main RCTs evaluating hyaluronic acid's (HA) effectiveness in periodontal treatment.SRP-Scaling and root planning; BOP-Bleeding on probing; PPD- Probing pocket depth; CAL- Clinical attachment level; CAF-Coronally advanced flap and GTR-Guided tissue regeneration

Table 2. Summary of Key Studies on Applications of Hyaluronic Acid in Peri-implant and Oral Wound healing

Author (Year)	Study Design & Sample Size	Clinical Application	HA Formulation / Concentration	Comparison / Control	Main Outcomes	Conclusion
Sahu et al. (2024)[19] role of HA[20]	Narrative review	Comprehensive periodontal applications	Various formulations (0.2–0.8 %)	—	Synthesized biologic and clinical evidence	HA safe and effective adjunct in soft-tissue healing
Singh et al. (2021)	Split-mouth RCT, n = 40	Free gingival graft donor site healing	HA (0.8%) gel topically	Placebo gel	↓ pain, ↓ erythema, ↑ healing index	HA reduced post-operative discomfort and improved repair
Al-Qutub et al. (2020)	Prospective study, n = 30	Peri-implantitis (non-surgical therapy)	0.8 % cross-linked HA gel after debridement	Debridement only	↓ PPD by 1.2 mm; ↓ bleeding index	Adjunctive HA improved soft-tissue healing
Sanz et al. (2019)	Animal trial (dog model)	Implant surface modification	HA-coated implants vs uncoated	Uncoated titanium	↑ bone-to-implant contact and bone density	HA coating enhanced osseointegration
Gupta et al. (2018)	RCT, n = 50	Post-extraction socket healing	0.2 % HA gel in socket	Standard care (no gel)	↑ epithelialization rate and granulation tissue formation	HA accelerated soft-tissue closure
Rossi et al. (2017)	RCT, n = 40	Peri-implant mucositis	0.2 % HA gel applied in peri-implant sulcus	Conventional chlorhexidine gel	↓ BOP, ↓ PPD at 3 months	HA comparable to CHX with superior tolerance

Notes for Table 2 Caption

Table 2. Summary of major studies evaluating hyaluronic acid (HA) in peri-implant therapy and oral wound healing. BOP – bleeding on probing; PPD – probing pocket depth; CHX – chlorhexidine; HA – hyaluronic acid.