Procedures Update

Hyaluronic Acid in Wound Management: An Update on Formulations, Mechanisms, and Clinical Applications

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Abstract

Introduction. HA underpins hydration, immune modulation, and matrix remodeling in wound healing. Its effects vary by molecular weight and formulation, with direct implications for clinical use. This update aims to analyzed and discuss the current knowledge on HA, with the objective of outlining its mechanisms of action and exploring the clinical implications of the various formulations used in wound care.

Methods. This update integrates key contributions (2000–2024) from PubMed, Scopus, and authoritative wound-care texts on the cutaneous use of HA in adult and pediatric patients. Evidence was organized to describe mechanisms, formulation characteristics (HA-only, HA+Ag, HA+AA, HYAFF scaffolds, injectable HA+6AA), and practice integration across acute and chronic wounds. No systematic review procedures were applied.

Results. High-molecular-weight HA shows protective and anti-inflammatory actions; low- molecular-weight HA promotes angiogenesis and immune activation. Clinically, HA-only topicals aid hydration and epithelialization; HA+Ag addresses bioburden; HA+AA supports stalled/ischemic beds; scaffolded HYAFF provides structure and sustained release for deep/exuding wounds; injectable HA+6AA augments remodeling in complex cases. A TIMERS-aligned framework supports step-up/step-down use and escalation when progression thresholds are unmet.

Discussion. HA is a formulation-dependent therapeutic that benefits wound outcomes when matched to phenotype and phase. Heterogeneity of products and outcomes limits cross-study comparability; head-to-head trials and standardized endpoints are priorities to refine indications across hospital and community pathways.

Keywords: Hyaluronic Acid, Skin Regeneration, Wound Healing, Molecular Weight, Topical Formulations, Chronic Wounds

Introduction

Hyaluronic acid (HA) is one of the main components of the extracellular matrix (ECM) and plays a central role in tissue regeneration processes. Thanks to its marked hydrophilicity, HA is capable of retaining large amounts of water, thereby creating a moist environment that supports the migration and proliferation of fibroblasts and keratinocytes-key cells in wound repair.1 This hydrated microenvironment not only sustains cellular viability but also facilitates the diffusion of nutrients and biochemical signals essential for skin regeneration.[1]

In the field of wound care, interest in HA has grown significantly in recent years due to its involvement in all key phases of the wound healing cascade. During the inflammatory phase, HA contributes to modulating the immune response, helping to control inflammatory infiltrates and limit tissue damage.[2] In the proliferative phase, it stimulates granulation tissue formation, collagen synthesis and neovascularization. During the remodelling phase, it supports the reorganization of the ECM and the re-epithelialization of the wound. These properties have justified its extensive clinical use in both acute and chronic wound settings, with documented benefits in terms of reduced healing time and improved scar quality.[3]

However, not all HA-based formulations share the same characteristics or exert equivalent biological effects. The properties of HA are strongly influenced by several variables, including molecular weight (MW), concentration, chemical structure (linear or cross-linked), source of origin (biotechnological or animal-derived) and the pharmaceutical vehicle used. Among these, MW is a key determinant of biological activity: high molecular weight HA (HMW-HA) is generally associated with barrier, anti-inflammatory, and protective effects, while low molecular weight HA (LMW-HA), which tends to accumulate under stress or injury, is more actively involved in immune activation, cell proliferation, and angiogenesis.[4,5]

The formulation type also plays a crucial role in clinical effectiveness. Gels, creams, sprays, powders, films or membranes differ in their ability to retain moisture, conform to the wound bed and deliver active ingredients. Therefore, the selection of a specific HA-based medical device must be guided by the wound's characteristics-such as size, depth and exudate level-as well as by the stage of healing and the clinical context.[6]

From an anatomical and physiological perspective, the skin represents the body's main reservoir of HA. Although it constitutes approximately 15% of total body weight, it contains over 50% of the total HA. In the dermis, HA contributes to elasticity and skin turgor, while in the epidermis, it plays a key role in maintaining the lipid barrier and ensuring cell cohesion (Table 1).[7,8]

Table 1. Physiological functions of HA in the Dermis and Epidermis. Adapted from Ciprandi G, Nicolosi B (2025).

DERMIS	EPIDERMIDIS
Hydration: Exceptional water retention ability, acting as a Natural Moisture Factor (NMF).	**Barrier Function**: Essential for maintaining the structure of the stratum corneum.
Elasticity: Connects collagen and elastin in the extracellular matrix.	**Interstitial Space**: Located in the 15-20 nm thick space between keratinocytes.
Intercellular Environment: Facilitates diffusion of nutrients, growth factors, and cytokines.	**Interaction with HA Receptors**: Maintains lipid barrier integrity.
Inflammatory Regulation: Helps control hydration during inflammation and embryonic development.	**Role in Keratinocyte Differentiation**: HA and CD44 contribute to lamellar body formation and lipid secretion (sphingomyelin, glycosphingolipids, phospholipids, cholesterol).
Elastic Structures: High-molecular-weight HA can form elastic structures.	**Antioxidant Protection**: Acts as a free radical scavenger, creating a viscous pericellular mesh around cells.

Today, HA is considered a cornerstone of advanced wound management, thanks to its multifunctionality, biocompatibility, and adaptability to diverse clinical needs. However, its effectiveness cannot be uniformly assessed: careful consideration of each formulation's characteristics is essential, integrating its use into a personalized therapeutic approach based on clinical evaluation and a thorough understanding of tissue repair biology.[9]

Given the numerous biological functions of HA and the growing availability of formulations for

cutaneous applications, a critical synthesis of the scientific evidence supporting its therapeutic use is timely. In particular, the structural and functional variability of HA requires an in-depth reflection on its actual impact on tissue healing processes.[10]

This update aims to analyzed and discuss the current body of knowledge on HA, with the objective of outlining its mechanisms of action and exploring the clinical implications of the various formulations used in wound care.

Narrative Framework for the Update

This article adopts a narrative and integrative approach, aimed at summarizing the most relevant biological and clinical insights concerning the use of HA in wound care. Rather than assessing the quality of individual studies, the focus was placed on identifying key mechanisms, formulation strategies, and practical implications that have shaped the current understanding and application of HA in clinical practice.

The literature overview was based on a selective exploration of scientific sources published between 2000 and 2024, retrieved from PubMed, Scopus, and authoritative textbooks in dermatology and wound healing. The search included combinations of terms such as "hyaluronic acid", "skin regeneration", "wound healing", "formulation", and "molecular weight". Additional references were identified through manual screening of citations within key articles and reviews. Only studies focusing on the cutaneous application of HA in experimental, preclinical, or clinical contexts were considered, while non-dermatologic uses were excluded.

Findings from both basic and applied research were synthesized narratively, with the intent to bridge experimental knowledge and practical wound care applications. The synthesis integrates molecular and physiological mechanisms with clinical and procedural evidence, highlighting how the structural and formulation diversity of HA translates into distinct therapeutic functions.

The following sections reflect this conceptual framework: Section 3 summarizes the biological rationale and mechanisms of action of HA in the three phases of wound repair; Section 4 discusses current formulations, clinical evidence, and procedural updates, integrating information from both commercial products and emerging technologies.

This structure aims to provide a clinically oriented overview, emphasizing translational insights and practical guidance rather than a quantitative evaluation of study quality.

Biological Rationale and Mechanisms of Action

HA was first discovered in 1934 by Meyer and Palmer in the vitreous humor of bovine eyes. The term "hyaluronic" combines "hyaloid" (vitreous) and "uronic acid," referring to its chemical nature. Initial studies in the 1950s by Karl Meyer elucidated the chemical structure of HA, and subsequent research through the 1960s and 1970s revealed its localization in tissues and complex conformational structure using X-ray crystallography and nuclear magnetic resonance experiments. For a long time, HA was thought to be an inert ECM component, until pivotal studies by Hardingham and Muir demonstrated its biological functions through specific receptor interactions, fundamentally shifting its role from structural filler to dynamic signalling molecule in tissue repair and inflammation.[11]

HA is a key component of the extracellular matrix (ECM), acting as a regulator of cellular behavior during tissue injury and repair. Its biological activity depends primarily on its molecular weight (MW), which determines its structural conformation, receptor affinity, and downstream signaling.[12-15]

The molecule consists of repeating disaccharide units of N-acetylglucosamine and glucuronic acid linked by β-1,4 and β-1,3 glycosidic bonds, forming a highly hydrophilic, viscoelastic polymer capable of retaining up to 1,000 times its weight in water (Figure 1).[16-18]

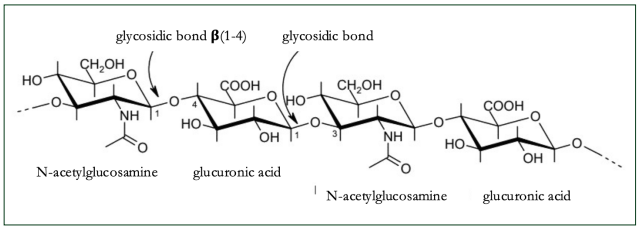

Figure 1. Chemical structure of HA, a linear glycosaminoglycan composed of repeating disaccharide units of N-acetylglucosamine and glucuronic acid. The units are linked via β(1→4) and β(1→3) glycosidic bonds, which confer the molecule its viscoelastic and hydrophilic properties essential for biological function in connective tissues.

This unique structure contributes to a hydrated and oxygen-permeable microenvironment essential for cell migration, proliferation, and differentiation within the wound bed.19-21

HA interacts with a group of specific cell-surface receptors – CD44, RHAMM, TLR2/4, LYVE-1, and HARE – which regulate processes such as inflammation, angiogenesis, and extracellular remodeling.22-24 Among the three hyaluronan synthase isoforms (HAS1-3), HAS2 predominantly generates high molecular weight HA (HMW-HA), typically around 2000 kDa, responsible for protective and anti-inflammatory actions.25,26 Conversely, low molecular weight HA (LMW-HA), formed by enzymatic degradation through hyaluronidases (HAase) or oxidative stress, behaves as a danger-associated molecular pattern (DAMP) that promotes immune activation, fibroblast proliferation, and angiogenesis.27,28

The dynamic equilibrium between these forms underlies the triphasic role of HA in wound healing (Figure 2).

Figure 2. Role of HA during the three main phases of wound healing. In the inflammatory phase (1) initiates the immune response and prepares the wound site; the proliferative phase (2) supports tissue regeneration through the recruitment of fibroblasts and keratinocytes; the remodelling phase (3) leads to wound maturation and the formation of either normal or pathological scarring. Adapted from Ciprandi G, Nicolosi B (2025).[9]

HA and the Inflammatory phase

In the early inflammatory phase, HA synthesis increases rapidly.[29] Upon skin injury, HMW-HA fragments are released into the wound environment, including platelet-derived and circulating HA fractions.[30] These fragments bind fibrinogen, initiating the extrinsic clotting cascade.30 The massive release of HA saturates the wound site with fluid, causing oedema and tissue swelling and creating a porous matrix that promotes immune cell migration.[31,32]

This phase is driven by cytokines such as TNF-α, IL-1β, and IL-8, whose activity is facilitated by HA.[31] However, HA also modulates inflammation via the hyaladherin TSG-6, whose expression is upregulated by IL-1 and TNF-α in fibroblasts and immune cells.[33] TSG-6 binds HMW-HA, forming heavy-chain complexes that suppress neutrophil migration and inhibit plasmin activation through feedback mechanisms, thereby tempering the inflammatory response.[34,35]

HA and the Proliferative phase

As inflammation subsides, fibroblasts migrate to the wound, attracted by small HA fragments (6-20 saccharides) and growth factors.[36] These cells synthesize collagen and glycosaminoglycans (including HA), contributing

to ECM reconstruction.[37,38] The length of HA chains influences collagen subtype expression, affecting scar quality. Collagen provides tensile strength to the healing wound and is synthesized in multiple isoforms by fibroblasts.[36-38]

Granulation tissue forms as collagen and elastin build the fibrous scaffold, and HA fills intercellular spaces with a hydrated gel.[31] HMW-HA, due to its hydrophilicity, provides elasticity comparable to cartilage, which is crucial in areas subjected to mechanical stress (for example, joints and plantar surfaces).[33] Without HA's porous, hydrated matrix, granulation tissue would lack architectural stability.

Oligomeric HA also promotes angiogenesis by binding CD44 and stimulating matrix metalloproteinases (MMPs), enabling basement membrane remodeling and capillary sprouting.[39,40]

HA and the Remodelling phase

This final phase involves progressive tissue maturation and scar formation.[18] Fibroblast activity and ECM remodeling continue, with collagen synthesis and degradation reaching physiological equilibrium after approximately three weeks.[37,44] Although tensile strength increases gradually, it never matches that of uninjured skin.[37,45] Ultimately, HA and provisional matrix structures are resorbed and replaced by a dense, avascular collagen matrix. This disorganized collagen architecture results in lower mechanical performance compared with native dermis.[42]

Clinical correlation

The anti-inflammatory, viscoelastic, and angiogenic properties of HA make it a versatile biopolymer adaptable to specific stages of wound healing. High–molecular–weight HA (HMW-HA) formulations are suited for early, inflamed wounds due to their protective and immunomodulatory effects, whereas low–molecular–weight HA (LMW-HA) species promote cellular proliferation, angiogenesis, and wound closure. Cross-linked or esterified HA scaffolds extend residence time and provide structural support for chronic or deep wounds (Table 2).[46,47]

Table 2. Classification of HA based on molecular weight. The biological activity of HA varies significantly according to its MW (in kilodaltons-kDa), influencing its role in inflammation modulation, cell proliferation, angiogenesis, and tissue regeneration.

Type of HA	MW Range
Oligomeric HA (o-HA)	< 10 kDa
Low Molecular Weight HA (LMW-HA)	10–250 kDa
Medium Molecular Weight HA (MMW-HA)	250–1000 kDa
High Molecular Weight HA (HMW-HA)	> 1000 kDa
Very High Molecular Weight HA (vHMW-HA)	> 6000 kDa

Beyond molecular-weight classification, the Visual and Structural Classification of Natural and Variably Stabilized Hyaluronic Acids (ViSCNOVAS) provides a complementary framework to describe the morphological and functional variability of HA formulations. This system considers key parameters such as molecular-weight distribution, polymer chain architecture (linear versus cross-linked), degree of modification or esterification, and the resulting rheological behavior.48

According to the ViSCNOVAS model, HA formulations can be conceptually grouped into four progressive structural categories. The first category includes native, linear, non-stabilized HA, characterized by high purity and minimal chemical modification, primarily intended to enhance hydration and epithelial regeneration. The second category consists of hybrid or partially stabilized HA, in which chains of different molecular weights are combined to optimize viscoelasticity and persistence. A third category comprises cross-linked HA, designed to increase viscosity and resistance to enzymatic degradation, thereby prolonging its residence time and providing structural support in deeper or more complex wound environments. Lastly, chemically modified or esterified HA represents the fourth category, developed for sustained release, three-dimensional integration, and regenerative matrix support, particularly in situations requiring prolonged biomechanical stability and tissue integration.48

This classification underscores how HA's structural conformation directly influences its clinical performance, helping clinicians match molecular characteristics with therapeutic goals in wound management.

The distribution of HA molecular weights

also changes significantly under pathological conditions. Under physiological circumstances, tissues primarily contain high-molecular-weight HA; however, following injury or during inflammation, low-molecular-weight HA fragments accumulate and act as molecular danger signals, activating immune responses and stimulating fibroblast and endothelial activity. In contrast, high-molecular-weight forms exert epithelial protective functions, support tissue stability, and demonstrate anti-inflammatory and analgesic effects (Table 3).[49,50]

Table 3. Classification of HA based on its molecular weight, highlighting the typical molecular weight range, presence under physiological or pathological conditions, and biological roles. Each HA subtype – from oligomeric to very high molecular weight – exhibits distinct effects on tissue homeostasis, inflammation, and wound healing, reflecting its structural and functional diversity.

Type of HA	MW	Presence	Role
o-HA	< 10 kDa	Rarely detected in vivo, produced by intense degradation	May exert marked pro-inflammatory and pro-angiogenic effects but is not well characterized.
LMW-HA	10–250 kDa	Rarely present under pathological conditions	Enhances immune response, promotes cell proliferation, inflammation, collagen synthesis, and angiogenesis. Acts as a DAMP and may contribute to chronic inflammation.
MMW-HA	250–1000 kDa	In intermediate quantities, produced both by direct synthesis and partial degradation of HMW HA	May have mixed properties, balancing stimulation and modulation of inflammation.
HMW-HA	> 1000 kDa	2000 kDa is the most abundant	Counteracts LMW HA effects, promotes wound healing, maintains tissue stability, protects epithelial tissues, and exerts anti-inflammatory, antinociceptive, immunosuppressive, and anti-angiogenic effects. Interacts with receptors such as CD44 and TLR4, inhibits neutrophil migration via TSG-6.
vHMW-HA	> 6000 kDa	Present in smaller amounts; selectively produced by HAS2 in specific tissues	Amplified protective and anti-inflammatory effects, greater ECM stability and viscosity.

Such differentiation forms the biological foundation for the wide range of HA-based medical devices currently available for wound care, designed to leverage specific molecular and structural properties for targeted clinical outcomes.[51]

Practical implications and integration into clinical practice

The clinical translation of HA research requires a formulation-driven and context-specific approach. The biological versatility of HA – determined by its molecular weight, degree of stabilization, and pharmaceutical form – governs its therapeutic behavior and defines its optimal clinical application.[52] Consequently, integrating HA into wound-care pathways demands careful alignment between its structural and functional properties and the wound's pathophysiological stage, exudate level, and risk of infection.[53]

Decision-making framework for HA formulation selection

Building on the biological and clinical evidence summarized above, the practical use of HA in wound management should follow a formulation-specific and phase-oriented strategy. Selection must be guided by wound type, moisture balance needs, bioburden status, and predominant healing phase, ensuring that the chosen HA form supports physiological tissue repair while addressing local clinical priorities.[53]

The following framework provides a concise guide to help clinicians match each HA formulation to the most appropriate wound condition, enabling individualized, mechanism-based, and evidence-driven treatment planning.[54] Table 4 summarizes the recommended HA formulations according to wound characteristics, exudate level, and therapeutic objectives, offering a practical tool to facilitate structured integration of HA into modern wound-care protocols.

Table 4. Summarizes the recommended HA formulations according to wound characteristics and clinical rationale.

Wound type	Recommended HA formulation	Rationale clinical
Acute clean superficial (abrasions, surgical incisions)	LMW-HA cream or gel (0.2-0.25%)	Promotes hydration, epithelialization, and pain relief.
Exudative or infected wounds	HA+Ag (Connettivina Plus®, Hyalosilver®)	Provides antimicrobial and anti-inflammatory action; controls bioburden.
Chronic dry or necrotic wounds	HA+4AA gel or powder (Vulnamin®)	Supports collagen synthesis, maintains moisture, reactivates chronic wounds.
Deep or full-thickness wounds	Cross-linked or esterified HA scaffold (HYAFF®-based, Hyalomatrix®, Hyalosafe®)	Provides 3D structural matrix for dermal regeneration and sustained HA release.
Mixed or delayed healing lesions	Injectable HA+6AA (Vulnamin® Inj)	Enhances tissue remodeling and localized repair in chronic or complex wounds.
Mucosal or oral lesions	HA+4AA spray or mouthwash (Mucosamin®)	Facilitates rapid mucosal repair and pain reduction; suitable for pediatric and oncologic care.

This framework underscores the importance of integrating HA formulations into standardized wound-care pathways, aligning their application with the Tissue, Inflammation/Infection, Moisture balance, Edge advancement, Regeneration, and Social factors (TIMERS) model and adapting their use to the clinical setting.[55]

Integration of HA into Wound Care Protocols

HA-based dressings can be integrated into standard wound-care algorithms, particularly after wound bed preparation according to the TIMERS framework. Within a TIMERS-oriented workflow, HA selection should correspond to the predominant barrier to healing in each phase.[56]

T (Tissue): after wound bed preparation, sodium hyaluronate combined with collagenase may be used when selective enzymatic debridement is required; once slough and necrosis are reduced, transition to LMW-HA gel or cream (≈0.2-0.25%) to maintain moisture and support keratinocyte migration.[59]

I (Inflammation/Infection): in contaminated or at-risk wounds, prefer HA+Ag (cream, spray, gauze) to couple moisture balance with bioburden control; in overt infection, HA+Ag can support local management while systemic therapy is optimized and reassessed every 48-72h.[26-27]

M (Moisture): for dry or stalled wounds, escalate to HA+AA (gel, cream, or powder depending on exudate) to rehydrate the wound bed and support collagen synthesis; for highly exudative wounds, pair HA powder or HYAFF® scaffolds with absorptive secondary dressings.[24,46,47]

E (Edge): when epithelial advancement is limited, use cross-linked or esterified HA scaffolds (for example, HYAFF® films, membranes, sponges) to provide a 3D matrix and support cell migration at wound edges.[21-23]

R (Regeneration): in chronic, deep, or metabolically stagnant wounds, injectable HA+AA may be added peri- or intralesionally to stimulate dermal remodeling in synergy with topical HA.[24]

Introducing HA across care pathways: hospital, community, and telemonitoring settings

In peri-operative and post-surgical contexts, start LMW-HA immediately after cleansing or closure on clean incisions to reduce pain and support re-epithelialization; upgrade to HA+Ag if device-related risk or early signs of critical colonization emerge.[26,27,52] In acute burns and superficial trauma, transparent HYAFF® films (for example, Hyalosafe®) help maintain a moist, semi-occlusive environment with easy inspection, then transition to LMW-HA as exudate subsides.[21–23,46,47]

For chronic-wound clinics or home care, embed HA in the standard visit: a) after debridement, initiate HA+AA for dry/ischemic beds or HA+Ag for bioburden; b) reassess weekly with objective criteria (area reduction, pain, exudate class) and step-down to HA-only when stable.[26,27,54] In pediatric care, prioritize non-stinging, easy-to-apply formats (sprays, films, soft gels) and minimize dressing changes; telemonitoring (photo audits, exudate scoring) can support titration between HA+Ag and HA+AA, documenting decisions against TIMERS checkpoints.[58]

When wound improvement is insufficient – for

example, when < 30% reduction in wound area is observed after 4 weeks of appropriate therapy – escalation should be initiated. This may include transitioning to scaffolded HA dressings and/or adding peri- or intralesional HA combined with AA or referring the patient for adjunctive or multidisciplinary interventions.[27,54]

Integrating HA with complementary wound-care strategies

Always prepare the wound bed first: mechanical/sharp or autolytic debridement; if dense fibrin persists or pain limits sharp debridement, use sodium hyaluronate + collagenase short-term, then switch to regenerative HA once clean.[59] Apply an antibiofilm routine (cyclical cleansing and contact-layer renewal) and, where risk is high, deploy HA+Ag for 7-14 days before de-escalating to HA-only or HA+AA.[26,27]

With Negative Pressure Wound Therapy (NPWT), place a non-adherent HA interface (LMW-HA gel/sheet or HYAFF® veil) or HA+AA over fragile structures to reduce adherence and support granulation; in deep cavities, HA+AA or HYAFF® sponges/membranes can act as a scaffold under NPWT.[57] Align dressing choice with the evolution of exudate: HA powder for heavy exudate, then gels/creams/films as moisture normalizes, and edge-focused HA scaffolds in the epithelialization phase.[21-23,46,47,54]

Follow a step-up/step-down approach: start with an HA formulation matched to the predominant TIMERS barrier; if bioburden or poor edge progression persists, escalate to HA+Ag or to scaffolded/injectable HA. Once the wound bed is clean, pain is reduced, and edges advance, de-escalate to HA-only formulations. Non-progression (≥70% residual area at 4 weeks) or red flags (ischemia, osteomyelitis, uncontrolled edema) should trigger multidisciplinary review.[27,54]

HA, being a natural (bio)polymer, is widely employed as a biomaterial in the development of wound dressings. Its non-toxicity, biodegradability, biocompatibility, gas permeability, and ease of application support safe use even in pediatric and chronic-care settings.[58] Despite these advantages, clinical and commercial use still presents limitations – potential impurities from extraction, higher production costs, limited mechanical stability in some vehicles, and variable bioactivity without adjuncts – driving the development of a broad range of solid and semi-solid HA dressings tailored to specific healing stages.[52-54]

Product-based recommendations and clinical scenarios

The growing variety of HA-based medical devices available for wound management necessitates formulation-specific decision-making based on wound characteristics and treatment goals.[60] Tables 5 and 6 summarize the principal commercially available HA products, classified according to formulation type (solid scaffolds vs topical preparations), concentration, and clinical indications.[52-54]

The choice of a specific product should be guided by key wound parameters – including depth, exudate level, infection risk, and healing phase – as well as by the clinician's therapeutic objectives. Each formulation offers distinct handling properties and biological effects, enabling personalized treatment strategies aligned with the TIMERS framework and tailored to the clinical scenario.[26-55]

Solid and scaffolded HA formulations such as sponges, films, and membranes are particularly indicated for deep or exuding wounds where structural support and prolonged HA release are required. Hyalomatrix® and Hyalofill-F® are suitable for chronic ulcers, full-thickness lesions, and second-degree burns, providing a three-dimensional matrix that sustains granulation and dermal regeneration.[21-23,46,47] Hyalosafe®, a transparent HA film, is especially valuable for superficial or surgical wounds and partial-thickness burns, allowing continuous inspection and maintaining an optimal moisture environment.[21-23] HylaSponge® offers substantial absorbency and is indicated for bleeding or heavily exuding chronic wounds, combining exudate control with hydration of the wound bed.[21-23,46,47,61,62] These products are summarized in Table 5.

In addition to scaffolded formulations, numerous topical HA-based products are available in gels, creams, sprays, and powders, allowing treatment to be tailored according to wound type and exudate level (Table 6). Topical HA preparations are particularly suitable for acute, superficial, or post-surgical wounds, as well as for maintenance phases following advanced therapies.[60]

Pure HA creams and gels (for example, Connettivina®, Cicatridina®, Ialuset®) promote

Table 5. Solid scaffold HA-based wound dressings. Comparative table of main products by type, HA characteristics, concentration, and clinical indications. *NR: non reported.

Commercially Available HA-Based Wound Dressings	HA dressing type		HA characteristic	HA concentration	Indications for use	References
Hyalofill-F®	HYAFF® hyaluronan-based biodegradable polymers	Fleece wound dressing composed of HYAFF®	Partial benzyl ester derivative of hyaluronan	NR*	Treatment of chronic wounds, including diabetic foot ulcers	56, 57
Hyalomatrix®	HYAFF® hyaluronan-based biodegradable polymers	HA-based membrane	HYAFF® 11 is an HA-derivative, which is acquired via the esterification reaction of the free HA carboxylic group and benzyl alcohol	NR*	Treatment of full-thickness wounds, second-degree burns, venous ulcers, pressure ulcers, and chronic vascular ulcers	58
Laserskin®	HYAFF® hyaluronan-based biodegradable polymers	HYAFF® biopolymer-sheet	HYAFF®-based material that has a microperforated HA sheet, with diameter of 40 mm and 500 mm, made with a laser-drill	NR*	Treatment of acute and chronic wounds	59
Hyalosafe®	HA-based films		HYAFF®, a total benzyl ester of HA, which creates a transparent film that is impermeable to microorganisms, but permeable to water vapor	NR*	Treatment of moderate exuding wounds, surgery wounds and second-degree burns	58
HylaSponge®	HA-based sponges	Network system of huge group of HA molecular chains	Network structure of long molecular chains of HA, capable of absorbing and releasing large volumes of water	2,50%	Treatment of acute and chronic wounds (diabetic, leg, and pressure ulcers and bleeding wounds)	60

hydration and pain reduction in clean, non-infected wounds, supporting epithelial migration and maintaining an optimal moisture environment.[60]

For wounds at risk of infection or showing early signs of critical colonization, HA combined with silver (Connettivina Plus®, Hyalosilver Plus®, Ialuset Plus®) provides local antimicrobial action while preserving moisture balance and tissue protection.[61]

Formulations combining HA with AA (Vulnamin® line) enhance collagen synthesis, extracellular-matrix remodeling, and angiogenesis, making them suitable for chronic, dry, or ischemic wounds. They are available as gel, cream, powder, spray, and injectable preparations, enabling precise adjustment to wound depth and exudate level.[62]

Other specialized options include sodium hyaluronate combined with collagenase (Bionect® Start), which supports selective enzymatic debridement in fibrinous wounds, and HA combined with polynucleotides (Nucliaskin S®), which aims to enhance dermal regeneration by synergizing HA hydration with nucleic-acid-mediated trophic activity.[63]

These products and their indications are summarized in Table 6.

Table 6. Topical liquid or semi-liquid HA-based wound dressings. Overview of the main commercially available products, including pharmaceutical form, HA characteristics, concentration, and principal clinical indications. *NR: non reported; **Percentage calculated from the concentration described in package leaflet.

Commercially Available HA-Based Wound Dressings	Dressing Type	HA characteristic	HA concentration	Indications for use
HA-only component				
Connettivina®	Gel	Sodium hyaluronate	2 mg/g (0.2%)**	Abrasions, grazes, superficial wounds, sunburns, minor burns and small cuts
	Cream	Sodium hyaluronate	2 mg/g (0.2%)**	Superficial skin injuries, such as abrasions, grazes, small cuts, minor burns and friction wounds
Hylase Wound Gel®	Gel	Sodium hyaluronate	2.5%	Acute and chronic wounds, including pressure injuries, 2nd and 3rd burns, and diabetic ulcers
Ialuset®	Cream	Sodium hyaluronate	0,2%	Non-infected wounds and burns, with or without exudate, leg ulcers, including those of venous origin, fissures, fistulas, bedsores, post-operative wounds, abrasive skin diseases and abrasions of chemical-physical origin
	Gauze	Sodium hyaluronate	0,05%	
HA-Based combination formulations				
Connettivina plus®	Cream	Sodium hyaluronate + Argentic sulfadiazine	10 mg/mL (1%)**	2nd and 3rd degree pressure injuries
Cicatridina®	Cream	Sodium hyaluronate + Almond oil	0.2%	Irritations and redness, superficial lesions (cracks, scratches, abrasions, erythema, superficial cuts), deep lesions (surgical wounds, 1st and 2nd degree burns, bedsores, ulcers)
	Spray	Sodium hyaluronate +Aluminum octenyl succinate + Almond oil	0.2%	Abrasions, lacerations, 1st and 2nd degree burns, surgical wounds, bedsores and ulcers
Vulnamin®	Cream	Sodium hyaluronate + 4AA (Gly, L-Pro, L- Leu, L-Lys)	1.33%	Chronic ulcers or damaged dermal areas
	Gel		2%	Necrotic or dry wounds
	PWD (Powder)		20%	Skin injuries of various origins with moderate to heavy exudate, even when colonized.
	Spray (Fluid gel)		1.33%	To prevent and treat early-stage or initial skin lesions
	INJ (Injectable liquid)	Sodium hyaluronate + 100 mg 6AA (Gly, L-Pro, L- Leu, L-Lys-L-Val-L-Arg)	1%	Direct applications in chronic wound environments and in the presence of delayed healing
Ialuset® Plus	Cream	Sodium hyaluronate+ Argentic sulfadiazine 1%	0.2%	Infected wounds and burns, dermatological conditions of bacterial origin or predisposed to the development of secondary infections
	Gauze	Sodium hyaluronate+ Argentic sulfadiazine 1%	0,05%	
Bionect® Start	Fluid ointment	Sodium hyaluronate + Collagenase (≥ 2.0 nkat/g)	0.2%	Used to remove harmful agents, abrasions, and restore skin integrity
Nucliaskin S®	Gel	Sodium hyaluronate + Polynucleotides HPT® +Vit E	NR*	Ulcers of lower limbs
Hyalosilver Plus®	Spray	Sodium hyaluronate + Metallic silver + Vit E	0.25%	Acute and chronic wounds at risk of infection or already contaminated, especially in the presence of exudate.

The diversity of HA-based products reflects the multifunctional nature of this biopolymer, with roles ranging from structural support and hydration to modulation of inflammation and tissue repair.[60] The clinical application of HA in wound management is closely linked to its physicochemical profile, as differences in molecular weight, degree of stabilization, and formulation design not only dictate biological activity but also influence handling properties and appropriate clinical setting.[61]

LMW-HA, characterized by high solubility and rapid diffusion, is ideally suited for superficial or early-stage wounds where hydration and epithelial stimulation are priorities. Its rapid absorption and ease of application make it advantageous in outpatient and home-care pathways requiring frequent dressing changes.[60,61]

Conversely, HMW-HA and vHMW-HA formulations provide greater viscosity, persistence, and mechanical protection, making them particularly useful in inflamed or exudative wounds and in post-surgical settings where prolonged moisture balance and reduced dressing frequency are required.[4,5,61]

Cross-linked and esterified HA derivatives offer prolonged residence time and enhanced structural integrity, which favors their use in deep or full-thickness wounds and in combination with advanced therapies such as NPWT, where they act as three-dimensional scaffolds promoting dermal regeneration and controlled exudate management.[21-23,57,62]

Formulations combined with bioactive components further refine clinical use: HA+Ag preparations are indicated for contaminated or high-risk wounds due to their ability to modulate bioburden while maintaining moisture balance,[26,27] whereas HA+AA formulations support metabolic activity, collagen synthesis, and re-epithelialization in chronic or ischemic wounds.[24,63,64] Injectable HA blends, such as HA combinated with six AA (HA+6AA), expand the therapeutic potential by offering peri- or intralesional stimulation of remodeling pathways in complex or non-healing wounds.[63,64]

In this context, HA structure and composition should not be considered mere chemical variations, but determinants of therapeutic context, frequency of application, and integration into multidisciplinary care pathways.[54] A rational selection of HA formulations requires alignment between physicochemical features, wound pathophysiology, clinical setting, and patient-specific factors, such as pain tolerance, exudate level, and capacity for follow-up care.[55]

Accordingly, different formulations serve distinct therapeutic functions: scaffolded HA for structure and regeneration, HA+Ag for infection risk, HA+AA for chronic or stalled wounds, and HA-only formulations for hydration and maintenance.[26,27,54] This framework supports the integration of HA-based products into wound care protocols according to healing stage and care environment, from acute hospital settings to community-based and pediatric pathways.[58]

Despite these advances, ongoing research continues to explore new HA-based scaffolds and hybrid systems incorporating antimicrobials, anti-inflammatory agents, or growth factors to enhance epithelialization, angiogenesis, and remodeling.[65-67] As topical HA formulations evolve – differing in concentration, pharmaceutical form, and co-components – clinical outcomes may vary substantially, even when HA represents the primary active ingredient. Therefore, appropriate product selection requires consideration of multiple formulation-related variables already discussed, including molecular weight, concentration, delivery system, and adjunctive ingredients.[60-64]

Limitations and future directions

The present update has several methodological and translational limitations that must be acknowledged. First, the heterogeneity of the available evidence represents a major constraint. Studies on HA in wound care encompass a wide variety of formulations differing in molecular weight, concentration, degree of cross-linking, and combination with other bioactive compounds. This variability complicates the comparison of outcomes and makes it challenging to attribute clinical effects to specific HA characteristics.

Second, few head-to-head comparative studies exist to directly evaluate the relative effectiveness of different HA-based products or formulations. The absence of standardized protocols for application, dosing, and follow-up further limits reproducibility and cross-study comparability. Outcome measures are also inconsistently reported, often mixing subjective clinical impressions with heterogeneous healing endpoints, which weakens the strength of

evidence and impedes meta-analytic synthesis.

Moreover, most studies are single-center and exploratory, with small sample sizes and limited external validity. There is a general lack of data on cost-effectiveness, long-term outcomes, and real-world performance of HA dressings in diverse clinical settings, including community and home care.

Finally, transparency regarding the exact composition and rheological properties of commercial formulations remains limited, hindering the interpretation of product-specific results and the translation of findings into practice.

Future research should therefore focus on well-designed, adequately powered randomized controlled trials comparing standardized HA formulations; on the development of shared outcome measures aligned with international wound-healing frameworks; and on the integration of real-world data and economic analyses to better define the value and sustainability of HA-based wound management strategies.

Conclusions

HA is a fundamental component of the ECM and exerts pivotal functions throughout all stages of wound healing – from inflammation modulation to cellular proliferation and tissue remodelling. Its biological performance is determined by molecular weight, structural configuration, and formulation design, which together shape its interaction with the wound microenvironment.

Topical and scaffold-based HA formulations have consistently demonstrated the ability to maintain hydration, promote granulation and epithelialization, and accelerate wound closure in both acute and chronic lesions. Nevertheless, therapeutic outcomes vary considerably depending on HA concentration, pharmaceutical form, co-formulants, and wound-specific variables such as depth, exudate level, and infection status.

Given this heterogeneity, the clinical use of HA should rely on an individualized, evidence-informed selection process that aligns formulation characteristics with the wound's pathophysiological phase. The current lack of standardized comparative studies and shared outcome measures, however, limits the ability to establish formulation superiority or develop universal treatment algorithms.

Future investigations should therefore prioritize head-to-head clinical trials, cost-effectiveness analyses, and real-world evaluations integrating molecular, clinical, and patient-reported outcomes.

In summary, HA represents a versatile and biocompatible biomaterial that – when rationally selected and applied within structured wound-care pathways – can substantially enhance healing quality and patient comfort across diverse clinical settings.

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