REVIEW

Hyaluronic Acid in Dermatology

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ABSTRACT

Hyaluronic acid (HA) is a major component of the extracellular matrix of the skin and plays an important role in the metabolism of the dermis. It has a key position in wound healing and tissue repair processes owing to its ability to maintain a humid environment favourable to healing and the stimulation of growth factors, cellular constituents, and the migration of various cells essential for healing. This review aims to describe briefly the physical, chemical, and biologic properties of HA, together with some details of the dermatologic indications of this unique molecule. (*SKINmed.* 2017;15:000–000)

In 1934, Karl Meyer and his colleague John Palmer isolated a chemical substance from the vitreous jelly of cow's eyes.[1] They proposed the name hyaluronic acid as it was derived from hyaloid (vitreous) and contained two sugar molecules, one of which was uronic acid.[2]

HA was first employed commercially in 1942 when Endre Balazs applied for a patent to use it as a substitute for egg white in bakery products.[2] It is present in the intercellular matrix of most vertebrate connective tissues, especially skin, where it has a protective, structure-stabilizing, and shock-absorbing role. For commercial purposes, it can be isolated either from animal sources such as synovial fluid, umbilical cord, skin, and rooster comb, or from bacteria through a process of fermentation or direct isolation. Its unique properties of biocompatibility, nonimmunogenicity, biodegradability, and viscoelasticity have rendered it an ideal biomaterial for cosmetic, medical, and pharmaceutical applications.

PHYSIOCHEMICAL AND BIOLOGIC PROPERTIES OF HA

HA is a nonsulfated glycosaminoglycan composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronidic β (1→3) bond.[3] HA has a β-sheet tertiary structure as a result of molecular aggregation and is stabilized by the presence of intermolecular hydrogen bonding.[4] It is one of the main constituents of the extracellular matrix and is therefore indispensable for the cellular framework.[5]

HA has a variety of physicochemical properties and encompasses a large volume of water, giving solutions high viscosity, even at low concentrations.[6] Because of its water-binding capacity, it is responsible for hydrating the skin and increasing its moisture content.[7] HA also plays an important role in exchange between cells and blood, as well as in cellular migration. Furthermore, recent studies have shown a role of HA in increasing cellular differentiation[7] as well as cellular motility, thus promoting wound healing.[8] Another function of HA is prevention of cellular damage from free radicals, which have an important role to play in skin aging.[9,10] Recently, HA has been shown to mediate various physiologic functions via interaction with binding proteins and cell surface receptors such as CD44[11–13] in the epidermis, suggesting that the molecule may be involved in cell function.[14]

HA in combination with other glycosaminoglycans, such as dermatan sulfate, chondroitin sulfate, and keratin sulfate in the skin, bind to water, and this induces the proteoglycans to become hydrated to such an extent that a gel-like system is formed.

DISTRIBUTION

HA is present in many places in the human body. It gives volume to the skin, shape to the eyes, and elasticity to the joints. In humans, HA is abundantly present in the skin,[15,16] accounting for 50% of total body HA,[17] vitreous of the eye,[18] umbilical cord,[19] and synovial fluid.[20,21] HA has also been found to be present in all tissues and fluids of the body, such as skeletal tissues,[22] heart

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valves,[23] lungs,[24] aorta,[25] prostate,[26] tunica albuginea, and corpora cavernosa and corpus spongiosum of the penis.[27]

METABOLISM

HA is synthesized by membrane-bound enzymes called HA synthases, which synthesize HA on the inner surface of the plasma membrane.[28] HA is then extruded through pore-like structures into the extracellular space.[29] The half-life of HA is variable, being 3 to 5 minutes in the blood, less than a day in the skin, and 1 to 3 weeks in the cartilage.[30,31] HA is degraded into fragments by hyaluronidases by hydrolyzing the hexosaminidic β (1–4) AUTHOR: SHOULD THIS HAVE AN ARROW INSTEAD OF A RULE BETWEEN '1' AND '4'?linkages between the N-acetyl-D-glucosamine and D-glucuronic acid residues in HA. In the presence of reducing agents such as ascorbic acid or thiols, ferrous, or cuprous ions, HA can also be degraded nonenzymatically by a free-radical mechanism.[32]

MEDICAL APPLICATIONS OF HA

HA finds application in various medical and surgical indications. The success of the medical applications of HA has led to the production of several successful commercial products. Various medical indications of HA are summarized as follows:

1. Osteoarthritis: HA provides a liberal amount of lubrication and mechanical support to joints affected with osteoarthritis. Administration of purified high-molecular-weight HA into orthopaedic joints AUTHOR: IS 'ORTHOPAEDIC JOINTS' CORRECT? SHOULD IT BE CHANGED TO 'OSTEOARTHRITIC JOINTS'? can restore the desirable rheologic properties and alleviate some of the clinical manifestations of osteoarthritis.[33,34]
2. Surgery and wound healing: Because of its viscoelastic and biocompatible properties, HA is used as a growth scaffold in surgery[35] and wound healing.[36]
3. Ophthalmic indications: HA is used in ocular surgeries for the implantation of artificial intraocular lenses and as a viscoelastic gel.[37–39]
4. Embryo implantation: HA has also been used as a culture medium for in vitro fertilization.[40,41]

HA AND THE SKIN

The highest concentrations of HA are found in connective tissues, and most HA (about 56%) is found in the skin. The estimated total amount of HA in human skin has been reported to be 5 g.[42] HA is present in the dermis (approximately 0.5 mg/g wet tissue) and the epidermis (approximately 0.1 mg/g wet tissue).43 The use of biotinylated HA-binding peptide44 has enabled the visualization of HA in the epidermis, mainly in the extracellular matrix of the upper spinous and granular layers, whereas in the basal layer HA is predominantly intracellular.[45]

The hydration of the skin critically depends on the HA-bound water in the dermis and in the vital area of the epidermis, while maintenance of hydration essentially depends on the stratum granulosum.[46] HA of the dermis along with the lymphatic and vascular systems regulates water balance, osmotic pressure, and ion flow, and functions as a sieve, excluding certain molecules, enhancing the extracellular domain of cell surfaces, and stabilizes skin structures by electrostatic interactions.[47]

DERMATOLOGIC INDICATIONS

Because of its viscoelastic properties and excellent biocompatibility, HA has been extensively used in cosmetology.[48] HA-containing cosmetic products restore moisture and elasticity to the skin, thereby achieving an antiwrinkle effect. Various dermatologic indications of this unique molecule are listed as follows.

Soft tissue augmentation

Soft tissue augmentation has revolutionized the treatment of the aging face. HA dermal fillers have frequently been used over the past decade for facial soft tissue augmentation because of their longevity, ease of use, and low immunogenicity.[49] Stabilized HA gels can stimulate collagen synthesis and inhibit collagen degradation, which can further contribute to their long-lasting effects.[50] Due to its nonanimal source, HA also has a minimal risk of inducing previously reported hypersensitivity reactions.[51–53] In cases of facial lines resulting from the loss of volume associated with aging, injectable fillers, which efface and support the static rhytides, are the most suitable treatment.[54] HA fillers from different manufacturers differ in characteristics such as total HA concentration, modulus, particle size, degree of crosslinking, percentage of crosslinked HA, amount of unmodified HA present, and extrusion force.[55] Various HA products used as fillers for soft tissue augmentation are:[2]

AUTHOR: FOR ALL THE DRUGS IN THIS LIST, PLEASE PROVIDE THE MANUFACTURER, CITY, STATE (WITHIN THE U.S.) AND COUNTRY (OUTSIDE THE U.S.). PLEASE ALSO INDICATE IF THESE SHOULD CARRY A 'REGISTERED', ®, symbol.

- Restylane, Perlane: biosynthetically produced by bacterial fermentation, with the advantage of being free from the risk of disease transmission or eliciting allergic reactions in hypersensitive patients.

- Dermalive: 14.5% HA and molecules of hydro-ethyl-methacrylate; consists of nonanimal, stabilized HA.
- Hyalaform: processed from the coxcombs of domestic fowl.
- Ac Hyal: 1% solution of the sodium salt of HA—a Japanese product that is available in Europe.
- Hylan Rofilan Gel: HA crosslinked with a natural acid.
- Reviderm – Intra: contains 40 to 60 m AUTHOR: PLEASE CLARIFY WHAT 'M' REPRESENTS.dextran beads of the Sephadex® type in hylan gel; nonimmunogenic, biocompatible, and biodegradable.

As per the American Society of Plastic Surgeons, around 2 million procedures using dermal fillers were carried out in 2012, 5% more than in 2011 and 205% more than in 2000.[56]

Adverse effects of HA dermal fillers can be injection related or substance related. Injection-related adverse effects are more common and consist of erythema, swelling, pain, itching, discoloration, and tenderness at the implant site.[2] Resolution is spontaneous within 1 or 2 days. Substance-related adverse effects are rare (fewer than 1 in 2000 treatments).[2] They are thought to be of a hypersensitive nature and consist of swelling and induration at the implant site.[2] A short course of oral steroids or intralesional hyaluronidase may be needed. A case of arterial embolization after the injection of dermal filler in the glabellar area has also been reported.[57]

Because HA fillers are costly, invasive, and painful, and may have side effects, there is a dire need for a topical, noninvasive, effective cosmetic treatment to replenish the skin with the lost HA. AUTHOR: PLEASE CONFIRM EDITS TO PREVIOUS SENTENCE. Recently, a study has shown the filling efficacy of a commercially available HA-based dermocosmetic treatment (Fillerina) AUTHOR: PLEASE PROVIDE MANUFACTURER NAME AND LOCATION DETAILS AND INDICATE WHETHER AN ® SYMBOL IS APPLICABLE. in the appearance of chronoaged skin in subjects showing mild to moderate clinical signs of skin aging on the face.[58]

Similar to the skin, lips are vulnerable to intrinsic and extrinsic factors that can change their appearance over time.[59] Treatment with HA-based dermal fillers can enhance the lips and perioral area, thereby reducing some of the signs of aging, and lip augmentation is currently recognized as one of the most common uses for these fillers.[60] Subjects undergoing lip enhancement procedures can expect treatment-emergent adverse events, such as swelling and bruising. These can affect daily activities and lengthen the time taken to return to social engagements while waiting for these side effects to resolve. It has also been observed that adverse events experienced by patients undergoing lip enhancement can be linked to factors relating to injection technique, such as the rapid injection of a large volume of filler.[61]

The midface region tends to be the primary area affected by age-related volume loss, clinically presenting as tear-trough deformities, molar hollowing, formation of a double convexity, and loss of cheek definition. Adding volume to the midface with filler provides a means of addressing all these signs of aging using a single procedure. HA fillers range in viscosity and enable the filling of wrinkles in addition to increasing cheek volume, thus replacing collagen as the "gold standard" among fillers. Recently, it has been shown that intradermal needle radiofrequency treatment with HA filler may be a more safe and effective method than HA filler alone for correcting midface volume deficit.[62]

In the temporal fossa, volume loss leads to an undesirable, gaunt appearance. By altering the temporal fossa and upper face with fillers, dermatologists are able to achieve a balanced and more youthful facial structure.[63] Many techniques have been described to inject filler into the fossa, including a "fanned" pattern of injections and highly diluted filler injection.[63] Complications of filler in the temporal fossa include bruising, tenderness, swelling, Tyndall effect, overcorrection, and chewing discomfort; the rare, more serious complications include infection, foreign body granuloma, intravascular necrosis, and blindness due to embolization into the ophthalmic artery.[63] Using reversible HA fillers, hyaluronidase can be used to relieve any discomfort felt by the patient.

Skin rejuvenation

Maintaining a youthful and pleasant appearance of the face in today's culture impacts quality of life for many patients. Facial aging is a complex and dynamic process. All people age differently as a result of imbalance, disharmony, and disproportion of the aging process between the overlying soft tissue and the underlying bony frameworks.[64] Even if the mechanism of skin aging has not yet been fully unravelled, it is evident that, during aging, the epidermis loses the principal molecule responsible for binding and retaining water molecules This results in loss of skin moisture and accounts for some of the most striking alterations of aged skin, including decreased turgidity, less support for microvessels, wrinkling, altered elasticity, and loss of face volumes, especially with regard to the cheekbones and lips.[65]

Recently, fillers have been developed to restore diminished skin volume and these are commonly used in the treatment of wrinkles. A variety of HA fillers are approved for the treatment of exaggerated nasolabial folds.[66] HA fillers offer good outcome,

are easy to inject, and have been associated with only a few adverse effects, such as mild pain, redness, and bruising. The major drawback of HA fillers is the relatively short duration of effect, necessitating frequent injections for maintenance.[67] Choi et al evaluated the clinical efficacy and safety of combination therapy comprising intradermal radiofrequency application and HA filler for the reduction of nasolabial folds wrinkles and demonstrated synergistic and long-lasting effects.[68]

A nasojugal groove or infraorbital hollow appears in the early stages of aging and is considered one of the landmarks of aging. It is characterized by a sunken appearance of the globe that results in the casting of a dark shadow over the nasal lower eyelid, giving the patient a fatigued appearance.[69] The use of HA dermal fillers to correct infraorbital hollows has evolved as a rapid nonsurgical option to improve the appearance of this area. However, due to the delicate and vascular nature of this area, several complications may occur with filler treatment in this area, such as edema, postinjection purpura, and arterial embolization of the retinal artery.[70]

For rejuvenation of the periorbital area, researchers have advocated the use of HA in conjunction with botulinum toxin.[71] The combination of botulinum toxin A and HA appears to rejuvenate the periorbital, temporal, glabellar, and crow's feet areas with minimal adverse effects.[72]

Recently, a clinical study demonstrated a significant improvement in the treatment of photoaging-induced wrinkles using the topical application of human growth factors and HA in women with facial photodamage.[73] HA may protect growth factors from degradation by proteases, making HA and growth factor a promising combination.[74] There is also some evidence that HA growth factors act synergistically to accelerate the healing process.[75] Therefore, topical products containing HA in combination with human growth factors might be particularly well suited for skin rejuvenation. Recently, mesotherapy with an intradermal HA formulation has also been used for skin rejuvenation.[76]

WOUND HEALING

HA extracts are safe and efficacious products for use in skin repair. Different gel formulations of HA have been used in patients with burns[77] and for the treatment of persistent ulcers.[78] HA has also been used in combination with platelet-rich plasma in the treatment of postoperative wound dehiscence and tendon exposure after surgery in patients with Morton's neuroma.[79]

Skin tissue engineering

Skin tissue engineering remains a valid option to treat difficult skin defects. The scaffold should act as a biodegradable template to mimic the natural skin microenvironment, containing the barrier function of the epidermal component and the mechanical stability and elasticity of the dermal component.[80] HA has been used as a component of scaffolds for wound healing. A number of animal studies using wound models have assessed the usefulness of HA-based scaffold.[81] These scaffolds, made up of various biologic components, promote dermal regeneration and wound healing. In a retrospective study, an HA sheet was used as scaffold with or without autologous cultured dermal fibroblasts after removal of a basal cell carcinoma on the face.[82] The use of autologous skin grafting on an HA scaffold in patients undergoing surgical scar removal facilitates better integration of the graft into the surrounding tissues, with dermis regeneration.[83]

En coup de sabre

En coup de sabre is a localized variant of scleroderma that presents as a linear, atrophic depression affecting the frontoparietal aspect of the face and scalp. The disfigurement may have a significantly negative impact on the patient's quality of life, and it is often the cosmetic aspect for which patients seek out care and intervention. Dermal filler treatments offer an attractive option as they are much less invasive and possess distinct advantages. HA filler may be safely and successfully used as monotherapy for temporary cosmetic improvement of en coup de sabre lesions.[84] The benefit is most prominent in well-selected patients who may experience atrophy but in whom the prominent feature is not tethering to underlying structures.84 There is a case report of HA filler used in conjunction with AlloDermTM AUTHOR: PLEASE PROVIDE MANUFACTURER'S DETAILS FOR ALLODERM AND CONFIRM WHETHER TM IS CORRECT.tissue matrix, which is essentially cadaveric dermis.[85] HA filler has been used in the correction of hemifacial atrophy seen in Parry-Romberg syndrome, a distinct but related variant of linear scleroderma.[86,87] However, these were both used in combination with other modalities: in one case autologous fat transfer, and in the other calcium hydroxylapatite filler.[86,87]

Diabetic foot

Diabetic foot ulceration is a major complication of diabetes mellitus. Current standard treatment for foot ulcers consists of restoration of adequate vascular supply, debridement, treatment of infections, and relief of pressure.[88] Several randomized controlled trials have evaluated the efficacy of HA-based wound healing techniques versus control in patients with diabetic foot.[89–91] HA is beneficial in treating diabetic wound ulcers by increasing the rate of wound healing, and is beneficial independent of the form in which the compound is applied to the wound.[92]

Mucositis

Virtually all patients receiving radio- and chemotherapy for cancer develop oral mucositis, a severe and highly debilitating condition. It is well established that the mechanisms initiating chemoradiation-induced mucosal injury, including oral mucositis, are linked to the production of reactive oxygen species.[93] It has been seen that the binding of high-molecular-mass HA to free radicals catalyzes the breakdown of HA into smaller fragments and thus inactivates reactive oxygen species.[94] Thus, it is possible that HA prevents the propagation of oxidative stress by sequestrating reactive oxygen species. A possible protective effect of a commercial formulation of HA enriched with amino acids (Mucosamin) AUTHOR: PLEASE PROVIDE MANUFACTURER'S DETAILS FOR MUCOSAMIN AND CONFIRM WHETHER TM OR ® IS APPLICABLE.against the damage induced by oxidative stress in vitro and in vivo has been investigated.[95] Data from a case series of patients undergoing radio/chemotherapy have strongly suggested that prophylactic use of the HA-based compound in the form of a spray may be effective in preventing the onset of oral mucositis.[95]

Melasma

HA in combination with hydroquinone and glycolic acid has been evaluated to be efficacious and safe in the treatment of melasma after topical application.[96]

CONCLUSIONS

HA is an essential component of the connective tissues, with the task of hydrating, lubricating, and returning elasticity to the skin, maintaining the shape of the tissues and strengthening their tone. It is now known to be the most important substance in "antiaging" research, mainly because of its safety and efficacy. The desire to turn back the clock while enjoying an active lifestyle has expanded the popularity of this unique molecule.

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