FIDIA ACADEMY
AWC ADVANCED WOUND CARE

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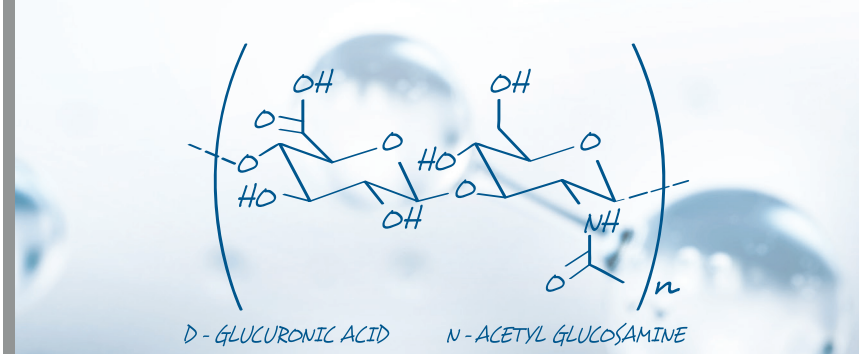
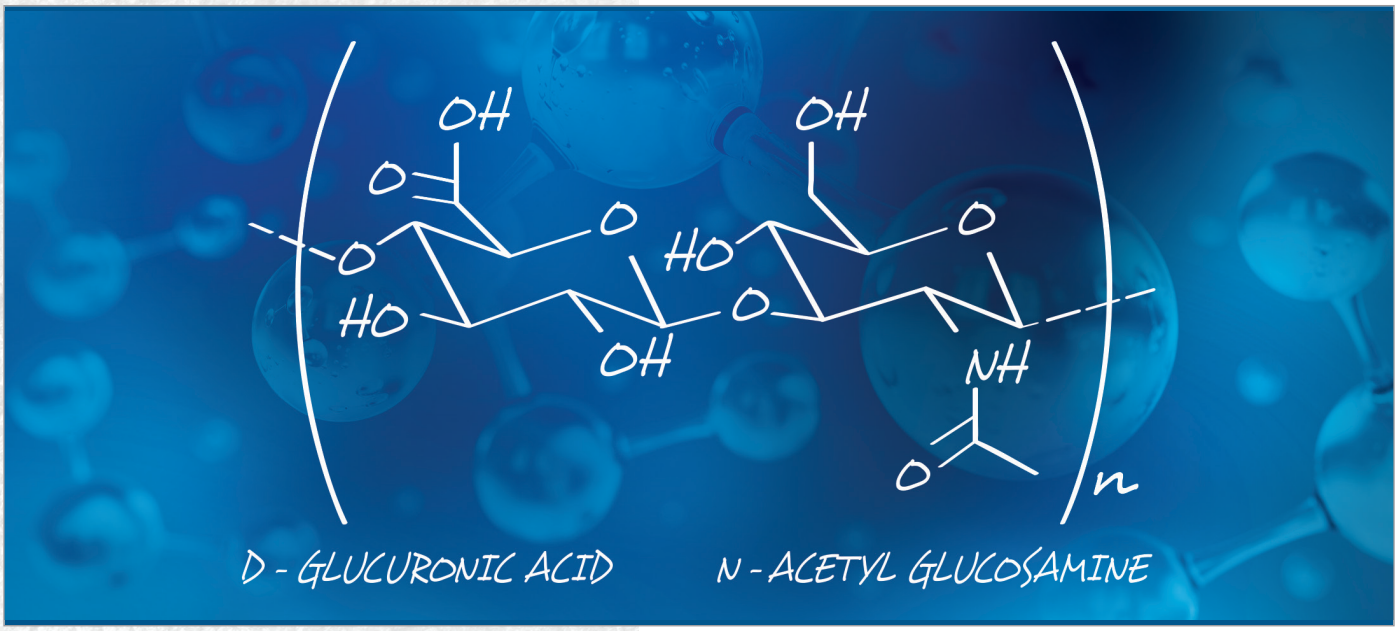


HYALURONIC ACID: KEY PLAYER IN WOUND CARE

Hyaluronic acid properties

Hyaluronic acid (HA) is a polymer of disaccharides composed of D-glucuronic acid and N-acetyl-D-glucosamine, linked via alternating ß-$_{1,4}$ and ß$_{1,3}$ glycosidic bonds.

Hyaluronic acid (HA) in wound care



Hyaluronan can have up to 25.000 disaccharide repeated units' length and range size approximately from 5000-20,000,000 Da *in vivo*[1]. HA is one of the major elements in the extracellular matrix (ECM) of vertebrate tissues. It is available in almost all body fluids and tissues, such as the synovial fluid, the vitreous humor of the eye and the hyaline cartilage. However, the largest amount of HA (7-8 g of hyaluronate per average adult human, or approx. 50% of the total in the body) resides in the skin, where it is present in both dermis and epidermis[2].

HA characteristics including its consistency, biocompatibility, and hydrophilicity have made it an excellent moisturizer in cosmetic dermatology and skin-care products[3].

Moreover, its unique viscoelasticity and limited immunogenity have led to its use in several biomedical applications such as viscosupplementation in osteoarthritis treatment, as in aid in eye surgery and for wound management[3].

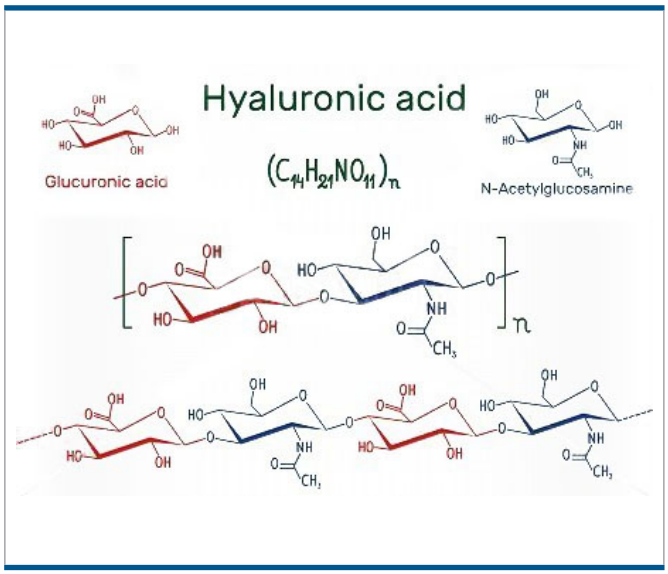
HYALURONIC ACID: MOLECULAR WEIGHT

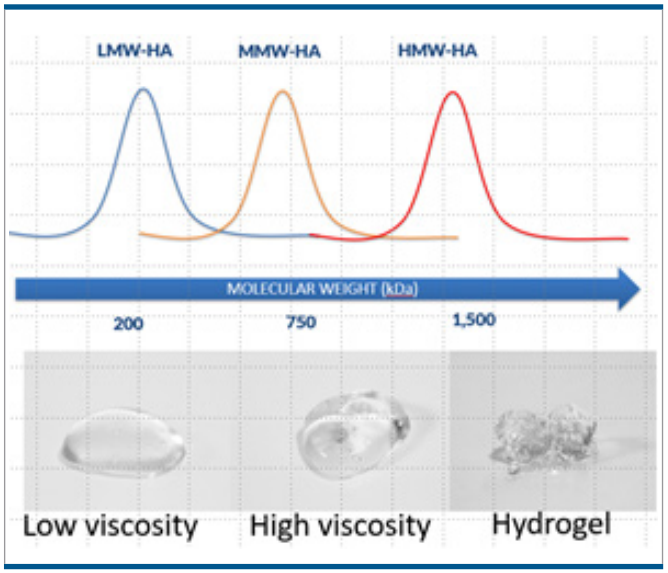
HA structural characteristics hinge on the random coiled structure in solution.

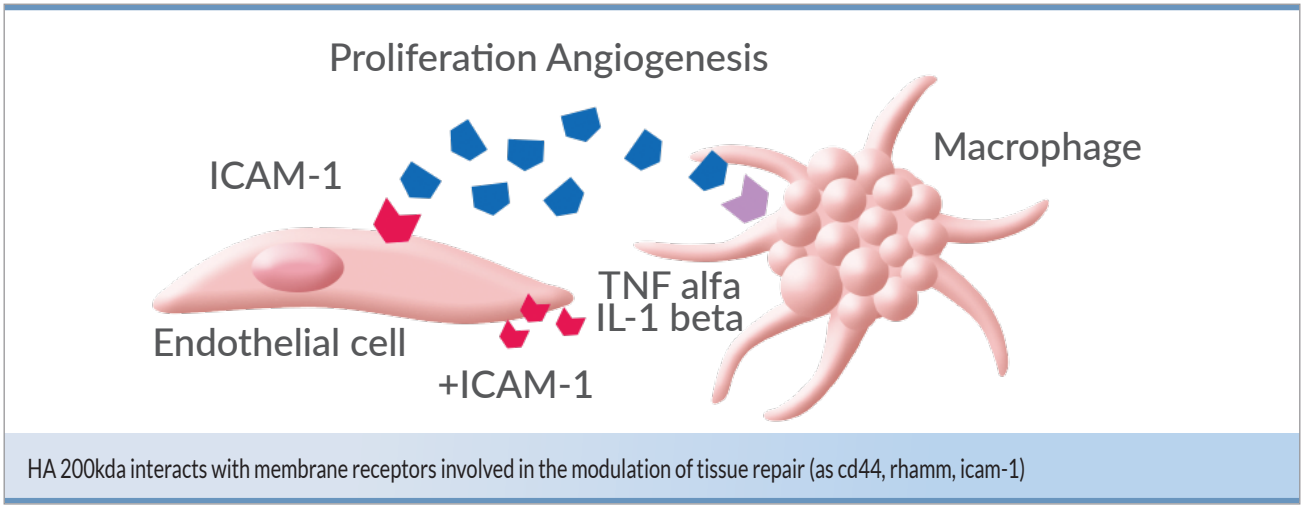
- **At very low concentrations**, chains entangle each other, leading to a mild viscosity (molecular weight dependent).
- On the other hand, HA solutions at **higher concentrations** have a higher than expected viscosity due to greater HA chain entanglement that is shear- dependent.

For instance, a 1% solution of high molecular weight HA can behave like jelly, but when shear stress is applied it will easily shear thin and can be injected via a thin needle[3]. As such, HA is known as a "pseudo-plastic" material. This rheological property of HA solutions has made HA ideal for lubrication in biomedical applications[3].

Furthermore, **HA plays a fundamental role in wound healing** and it should be remembered that HA fractions need to be highly homogenous in terms of molecular weight in order to exert their specific actions.







HA 200kda interacts with membrane receptors involved in the modulation of tissue repair (as cd44, rhamm, icam-1)

Low molecular weight HA (LMW-HA) (200 kDa average range) is the most appropriate fraction for wound healing, exerting a synergic effect with biologically active substances in the active process[4]. HA produces different effects on the basis of its molecular weight being also demonstrated by several clinical studies[5]. In fact, it has been shown that low molecular weight HA (200Kda average range) promotes wound repair from the earliest stages, while high molecular weight HA has no short-term effects, probably due to its higher initial viscosity[5].

HYALURONIC ACID HYDROPHILICITY AND LUBRICITY

As mentioned, HA is one of the most **hydrophilic molecules** in nature and can be described as nature's moisturizer[3]. When incorporated into a neutral aqueous solution hydrogen bond formation occurs between water molecules and adjacent carboxyl and N-acetyl groups. This imparts a conformational stiffness to the polymer, which limits its flexibility. The hydrogen bond formation results in the unique water bonding and retention capacity of HA.

Up to 6L of water may be bound per gram of HA[6].

As HA is **highly hydrophilic**, it is a polymer that is well suited to applications requiring minimal cellular adhesion. There is evidence that **hyaluronan separates most tissue surface** that slide along each other. Post-operative adhesions, which form between adjacent tissue layers following surgery, impede wound healing and often require additional surgical procedures to be repaired successfully. Barriers made from HA have been effectively used to prevent such adhesions from forming. Furthermore, the adhesion of bacteria to biomaterial can induce infections and constitute a great risk to the patient; HA has also been used to prevent bacterial adhesion to dental implants, intraocular lenses and catheters[3,6].

HYALURONIC ACID: BIOCOMPATIBILITY AND NON-IMMUNOGENICITY

As previously described, being a natural component of many human tissues,

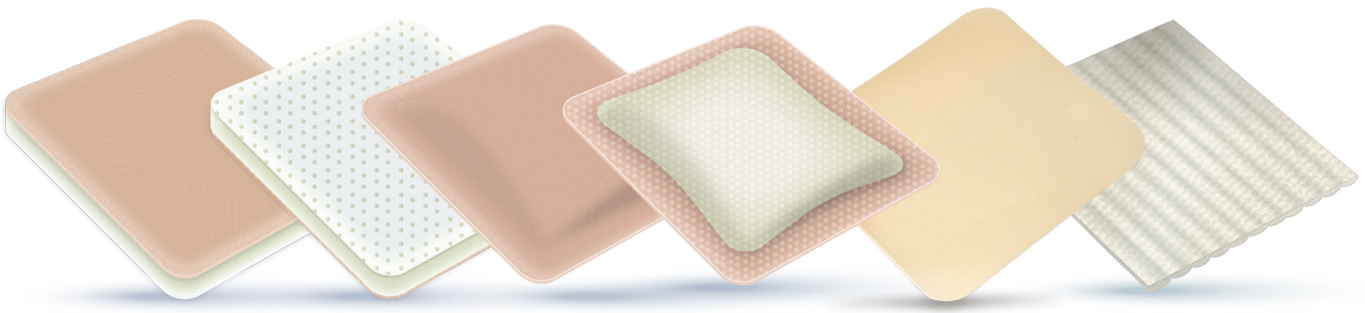
HA is highly biocompatible, a property that is essential for the application in biomedicine. Moreover, HA molecules present the same structure in all species and all tissues, therefore they never alert the immune system[2,3,6,7].

HYALURONIC ACID: INTERACTIONS WITH DRESSING MATERIALS

HA can be easily included within a gauze[8], but also exists as a gel/cream, microgranules and spray[9]. Therefore,

HA is known to be combined with other dressing materials, such as alginates, hydrogels, hydrocolloids and fibrin sheets[10] and PU foams[11]. Sodium hyaluronate can be combined with antiseptics such as iodine to reduce bacterial load. Nowadays, no particular interactions are known of HA with other wound dressings.

However, HA should not be used concomitantly with disinfectants containing quaternary ammonium salt, such as cetylpyridinium chloride (CPC), as it can precipitate in their presence[12].

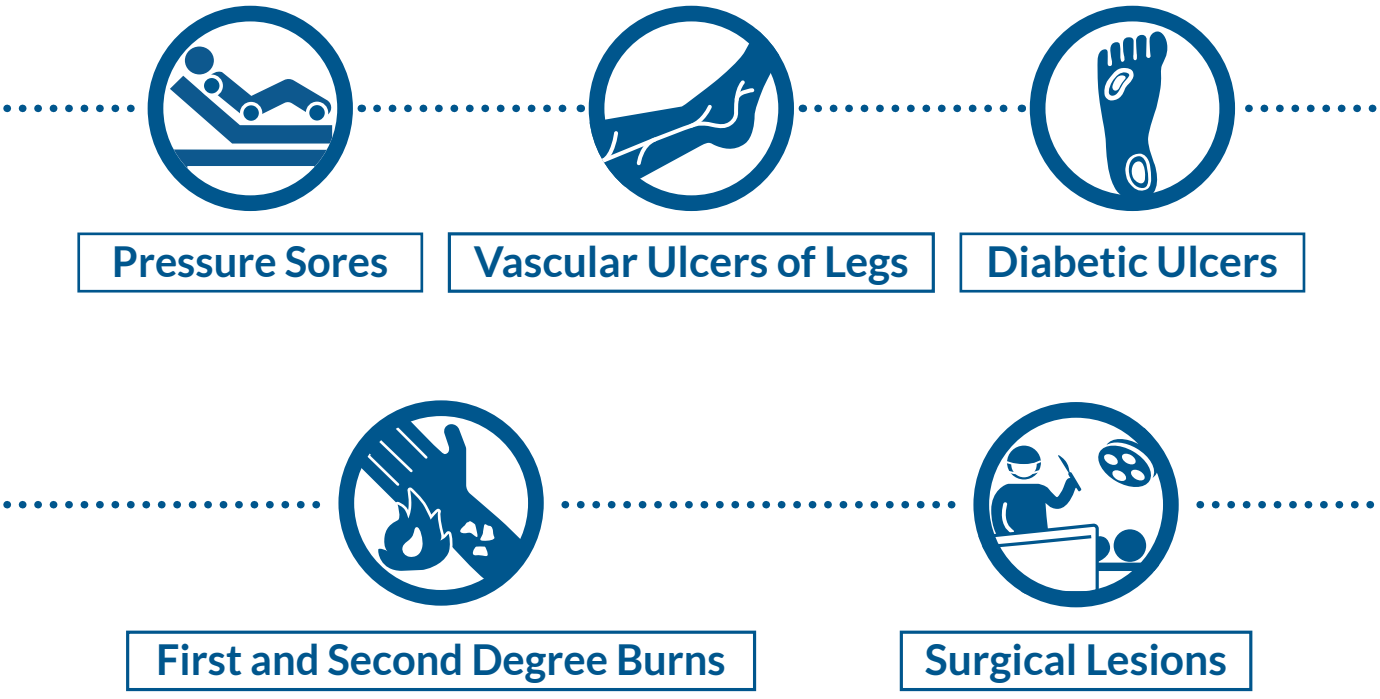


HYALURONIC ACID IN THE MANAGEMENT OF ACUTE AND CHRONIC WOUNDS

The scientific rationale for the development of wound dressings based on HA relies on the characteristics of the material, which has an important role in water homeostasis that could favor tissue hydration[1], indirectly supporting physiological cell migration in the wound bed.

Endogenous HA sustains wound healing and re-epithelization processes thanks to several actions including the promotion of fibroblast proliferation, migration and adhesion to the wound site, as well as the stimulation of collagen production. For these reasons, HA is used in topical formulations to treat skin irritations and wounds such as abrasions, post-surgical incisions, metabolic and vascular ulcers and burns. Currently, HA derivatives and HA-based wound dressing, films or hydrogels enriched with other therapeutic agents are being evaluated in order to understand if the cicatrization process could be further enhanced[13].

Topical HA is routinely used in the local treatment of acute and chronic wounds. Several clinical trials and systematic reviews have confirmed that HA, formulated as a cream or as cream-impregnated gauze pads for topical use, supports rapid wound healing in patients with impaired healing, not only suffering from chronic wounds, but also from acute lesions such as burns and epithelial surgical wounds[14]. HA has two very important functions in wound healing, contributing to cell proliferation and migration. First, HA provides a temporary structure in the early stages of the wound. This structure helps facilitate the diffusion of nutritional supplies and helps rid the wound of waste products from cell metabolism. Second and mostly important, HA is closely involved in keratinocyte (cell type of the epidermis or outermost layer of the skin) proliferation and migration. A systematic review performed by Voigt et al. evaluated several clinical studies to determine whether HA and its derivatives, used as a therapy, provide a clinically beneficial healing effect in burns, epithelial surgical, and chronic wounds vs. other therapies or placebo. There appears to be an overall positive effect of HA in the healing of chronic wound ulcers of various etiologies, burns, and epithelial surgical wounds no matter the form in which HA is delivered topically (i.e., pad, cream, substrate) with eight of the studies identified in the comprehensive search performed showing a significant improvement in the healing rates (with either complete healing or a reduction in wound size). Moreover, several clinical evidences support the positive healing effect of HA in patients presenting with venous leg ulcers, burns, and diabetic foot ulcers. What appears to be most interesting in these findings is that healing in the most difficult to treat ulcers among chronic wounds (i.e., diabetic foot ulcers) is accelerated with HA vs. using HA in other types of ulcers that were studied, a surprising finding considering the pathology of diabetes[15].



FIDIA FARMACEUTICI: experience and know-how with hyaluronic acid 200kda fraction in wound care

Fidia Farmaceutici S.p.A has more than 50 years' experience in production of medicinal products and medical devices based on hyaluronic acid and the effects of low molecular weight HA (200kDa) 0.2%, in the management of wounds of different origin, has been widely disentangled through clinical studies, here below discussed.

Therefore, the performance of FIDIA HA 200kDa 0.2% in the management of wounds has been investigated in several studies, involving different type of wounds as:

- **Pressure sores**
- **Burns**
- **Surgery wounds**
- **Venous Ulcers, Arterial Ulcers and Metabolic Ulcers**

Pressure Sores

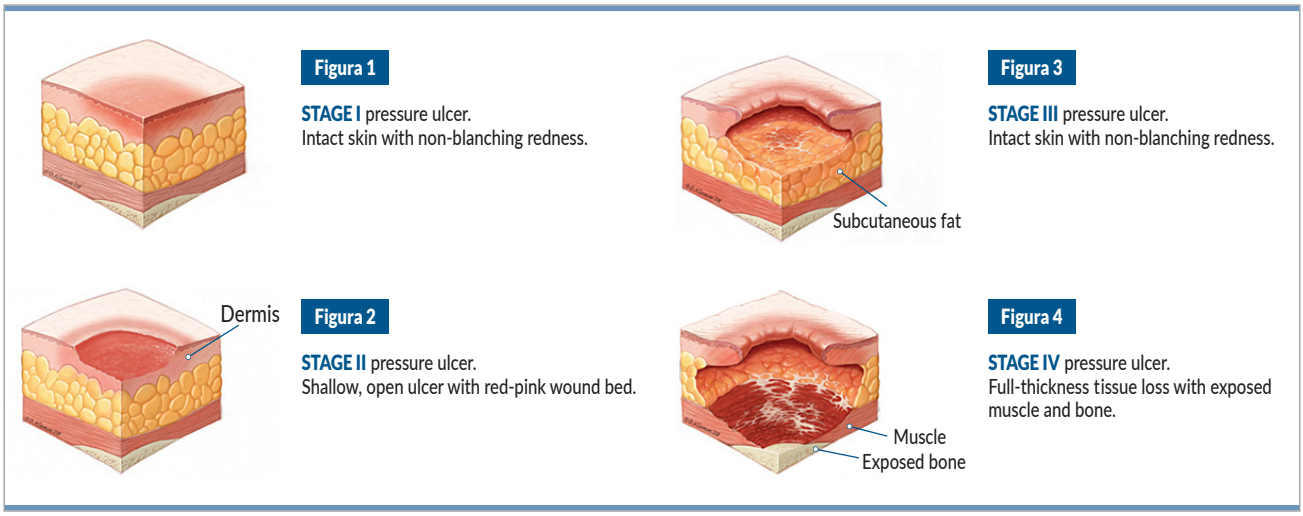
Pressure Sores, also known as bedsores, decubitus ulcers, are areas of injury to the skin or the underlying tissue, or both[16]. Although pressure ulcers can develop at any site, they occur more frequently over bony prominences, as previously reported. Patient position and degree of immobility can influence the site of involvement. The most common locations are the sacrum, coccyx and heels (when persons are in a supine position); the hips and ankles (when persons are lying on their sides); and the buttocks (when persons are seated). Less commonly involved are the earlobes, occiput, chin, elbow, scapula and knee[17].

Pressure ulcers are classified into four categories:

- **Stage I ulcers** are characterized by intact skin with non-blanchable erythema;
- **Stage II pressure ulcers** have partial- thickness skin damage with possible blister formation, but no subcutaneous tissues visible;
- **Stage III pressure ulcers** have full-thickness skin loss with subcutaneous fat exposed but no muscles, bones, or tendons visible;
- **Stage IV pressure ulcers** have tissue loss with exposure of muscles, bones, tendons, or vital organs[18].

An unstageable pressure sore refers to a wound with

an undetermined level of tissue injury because the entire base of the wound is covered by slough tissue and/or eschar. A deep tissue injury is a term recently proposed by the National Pressure Ulcer Advisory Panel (NPUAP) to describe a pressure wound that has tissue injury hidden below intact skin[19]. These wounds appear as deep bruises and have high potential for quick deterioration into a high-stage pressure ulcer.



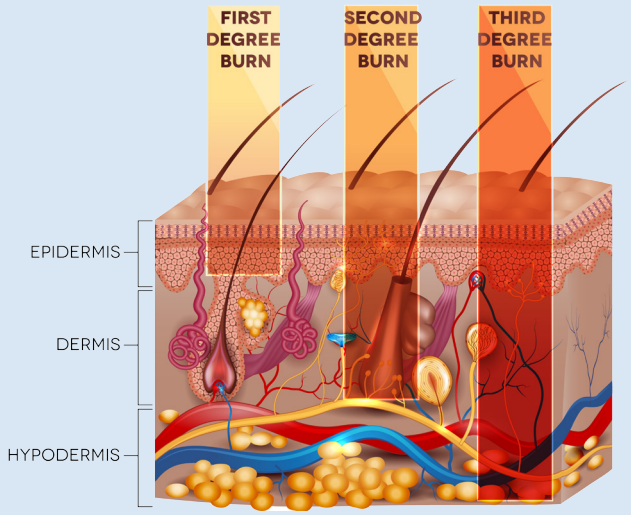
In these circumstances, treatment with FIDIA HYALURONIC ACID 200kDa 0.2% has improved the healing process ("restitutio ad integrum") of the skin. In fact, ***by providing a moist wound environment, FIDIA HYALURONIC ACID 200kDa 0.2% stimulates the formation of granulation tissue, promotes debridement of the wound, accelerates re-epithelization rates, and reduces treatment time[20]. The size of the lesion is significantly decreased with a subsequent reduction in re-epithelialization time[21,22]****. Furthermore, a marked improvement is found in the clinical appearance of the wound bed and wound edges with a reduction in pain in a high percentage of patients treated with FIDIA HYALURONIC ACID 200kDa 0.2%[21]. Additionally, in elderly patients affected by pressure lesions, Peghetti et al demonstrated an improvement or complete healing, of pressure ulcers (stage II-III) evaluated, was observed in 67% of patients at early follow up (10 days), increasing to 76% and 87% at 20 and 35-day control visits, respectively[23].*

Therefore, based on collected literature it can be concluded that exogenous FIDIA HYALURONIC ACID 200kDa stimulated and guides re-epithelization process in skin lesions,

with ischemic damage and senile involution, situation in which a lack of endogenous HA synthesis may occur, being not sufficient to guarantee a prompt and correct wound healing process[21].

Burns

Burns are one of the most common lesions. There are several causes of burns, ranging from direct heat (including flames and hot liquids) to chemical or electrical injury. Presentations differ depending on the cause, and severity is dependent on both contact time and the temperature to which the skin has been exposed[24]. Healing of a burn wound depends on the depth of the burn. Burn wounds can be classified according to the involvement of skin and deeper tissues as follows[25, 26]:



- **First-degree burn or epithelial burn:** skin is erythematic without vescication; like a sunburn, these lesions are erythematous, painful, and dry;
- **Second-degree burns:** involving epidermis and variable thickness of dermis. These are divided into:
- **Second-degree superficial**, where vescication and inflammation is seen in skin as only papillary dermis is involves;
- **Second-degree deep**, where eschar formation is seen as it involves deep reticular dermis.
- **Third-degree burn**, also known as full thickness burn: eschar formation is present in these burns.

In first-degree and second-degree superficial burns, healing is by primary intention. First-degree burns usually heal in 5 to 10 days[26]. Second-degree superficial burns heal from epithelium of hair follicle remnants, which are in plenty in the superficial dermis. These burns heal within 2 Weeks and generally do not cause scarring[25,26].

Treatment of second degree burns, both superficial and deep, with FIDIA HYALURONIC ACID 200kDa 0.2% has been demonstrated to be more efficient inducing a rapid re-epithelization compared to the control group[27]

The healing times, in relation to the type of lesion treated, appear greatly reduced with respect to the normal and testify in favour of the effective usefulness of this topical therapy. Furthermore, ***the action of FIDIA HYALURONIC ACID 200kDa 0.2% is manifested in short periods with a significant reduction of signs and symptoms related to the pathology of burns****. The rapid reduction of the diameter of the burn and consequently the equally rapid detersion of the lesion, demonstrated the positive action of FIDIA HYALURONIC ACID 200kDa 0.2%*[28]*. Due to the perfect local tolerability and the absence of general and systemic collateral effects shown in several studies ascertain that FIDIA HYALURONIC ACID 200kDa 0.2% have a good therapeutic index in the treatment of accidental burns*[28]*. Healing rate is dependent on general and local factors, among which humidity, temperature and oxygen, responsible for the microenvironment of the lesion. Burns treated with* ***FIDIA HYALURONIC ACID 200kDa 0.2% show a rapid formation of granulation tissue with a better debridement of the wound***[29,30,27]***, leading to faster re-epithelialization***[27]***, remission of objective signs (oedema and local infection) and pain***[31,29]*.*

FIDIA HYALURONIC ACID 200kDa 0.2% can be considered a great choice in the management of burns, not only in those superficial but also in the most profound thermal traumas characterized by contained surface extension[27]*. In fact, it has been demonstrated that HA represent an important curative aid in superficial epidermal-dermal burns; also in the deepest thermal trauma characterized by small extension, HA seems to respond completely thanks to its abilities of activating the tissue response*[27]*.*

Furthermore, it has been demonstrated that FIDIA HYALURONIC ACID 200kDa associated with silver sulfadiazine accelerated the repair process, with an average time interval taken for complete healing of 9.5 days, compare with the 14 days needed after the use of silver sulfadiazine alone. The differences between the two groups was statistically significant, thus supporting the efficacy of HA in the management of burns[32]***.***

Surgical Wounds

Surgical Wounds can be different types and sizes, depending on the nature and invasiveness of the surgical procedure the patient has undergone, from a surgical intervention aimed at removing a tumor to a simple procedure, such as surgical excision of a mole or of a hyperthrophic scar. Normally, surgical incisions are made with precision in an environment where aseptic and antiseptic techniques reduce the risk of infection, with the best instruments and the facility to control haemostasis. Following surgery, incisions are usually closed by fixing the edges together with sutures (stitches), staples, adhesive glue or clips. This process helps the cut edges heal together (healing by primary intention). However, a minority of surgical wounds are not closed in this way[33]. Infection of the surgical wound is a common post-operative complication, Surgical site **infections can be very serious causing ongoing health problems and associated healthcare costs, and even result in patient mortality**[34].

A study, conducted in 2007 by Ivanov et al, investigated the clinical application of FIDIA HYALURONIC ACID 200kDa 0.2% Gauze pads and Cream in the management of surgical wounds (cesarean section and episiotomy). A total of 47 patients were included; 27 had delivered by cesarean section and 20 had delivered via vaginal delivery with episiotomy. In 15 of the 27 patients who delivered by cesarean section, FIDIA HYALURONIC ACID 200kDa 0.2% Gauze pads was applied daily from day 2 to 7 following surgery; thereafter, these patients continued treatment at home with FIDIA HYALURONIC ACID 200kDa 0.2% Cream 3 times/day until day 40 post-partum. The other 12 patients who had delivered by cesarean section were treated with standard cleaning / disinfection and dressing. Ten of the 20 patients who had vaginal delivery and episiotomy were treated with FIDIA HYALURONIC ACID 200kDa 0.2% Cream 3 times/day; the other 10 patients were given standard disinfection of the episiotomy site.

Daily monitoring revealed faster management of edema, exudation, and infiltration in patients treated with FIDIA HYALURONIC ACID 200kDa 0.2%. Both FIDIA HYALURONIC ACID 200kDa 0.2% formulation, as gauze and cream, had excellent tolerability (only one patient experienced itching) and did not cause allergic reactions[35].

Moreover, another study performed using FIDIA HYALURONIC ACID 200kDa 0.2%, investigated the safety and the efficacy of HA 0.2% in two different formulation, as Cream and Gauze pads, in the management of both acute and chronic wounds. A total of 27 patients were included in the study and divided in two groups, one consisting of patients presenting flat lesions and the other consisting of patients having incisions (post-surgical wounds). A total of 30 lesions were treated: these were crural ulcers, burns and some acute wounds occurred after keloid excision, nevus excision and verrucae ablation. In the group with flat lesions, the wound size gradually reduced following treatment with HA 0.2% Cream or Gauze pads.

All of the surgical wounds treated with FIDIA HYALURONIC ACID 200kDa 0.2% healed completely within the first 2 Weeks of application.

After 6 weeks of treatment with FIDIA HYALURONIC ACID 200kDa 0.2%, 20 wounds healed completely; the other 18 (mostly chronic crural ulcers, n=16) had not healed completely, however a decrease in the wound size was observed. The investigators concluded that HA 0.2% was capable of significantly improving the healing of both acute and chronic uninfected wounds of different etiology, also providing pain relief.

FIDIA HYALURONIC ACID 200kDa 0.2% was very well-tolerated, and no adverse effect were recorded during follow-up. 74.1% of the patients reported tolerance to be "very good" and 25.9% of the patients reported it as being "good"[36].
In addition, the efficacy and safety of a two-week treatment with hyaluronic acid in patients after cryosurgery of a basalioma in the face/throat area was therefore investigated in the framework of a placebo-

controlled, double-blind study. The application of FIDIA HYALURONIC ACID 200kDa 0.2% achieved a markedly reduced duration of healing compared to placebo. All the parameters evaluated as healing, wound surface area and wound volume significantly decreased in the treated group, with a faster improvement compared to the placebo group[37].

Cutaneous Ulcers of Prevalently Vascular Origin

can be distinguished in vascular (venous or arterial), metabolic and pressure ulcers.

Venous Leg Ulcers (VLU)

Venous Leg Ulcers (VLU) are triggered by malfunction of venous valves causing venous hypertension in the crural veins (veins supplying the leg), which in turn increases the pressure of the capillaries and results in edema[8]. Patients with VLU may complain of tired, swollen, aching legs. The legs are typically edematous, often with hyperpigmentation of the lower part of the leg from chronic venous stasis. These ulcers are usually on or near the malleoli and in the distal medial leg. VLU can be painful, and are often colonized, and are often associated with comorbidites such as rheumatoid arthritis and diabetes[38]. The margins of the ulcers are generally irregular, with a shallow base.

Arterial ulcers

Arterial ulcers are due to a reduced arterial blood supply to the lower limb, and typically occurs over the toes, heels and bony prominences of the foot. Patients may relate intermittent claudication, pain in the extremities or buttocks with activity that is relieved by dandling the legs off the side of the bed. Physical examination reveals diminished or absent lower extremity pulses, trophic changes in the skin and decrease in hair growth. The ulcer appears “punched out”, with well demarcated edges and a pale, non-granulating, often necrotic base. The surrounding skin may exhibit dusky erythema and may be cool to touch, hairless, thin, and brittle, with a shiny texture. The toenails thicken and become opaque and may be lost. Gangrene of the extremities may also occur[39].

Metabolic Ulcers

Metabolic Ulcers, especially in the lower leg, can be caused by a number of existing metabolic disorders. Diabetic foot ulcers (DFUs) are the most common type of ulcers with metabolic causes. DFU is defined as a non- or poorly healing, partial- or full-thickness wound, located distal to the ankle in an individual with diabetes mellitus. Any foot wound in a patient with diabetes may become infected. Traditional inflammatory signs of infection are redness (erythema), warmth (calor), swelling or induration (tumor), tenderness and pain and purulent secretions. Some infected patients may

not manifest these findings, especially those who have peripheral neuropathy (leading to an absence of pain or tenderness) or limb ischemia (decreasing erythema, warmth, and possibly induration).

The skin changes consistent with ischemia include dry, thin, atrophied skin, dystrophic nails, abnormal wrinkling of skin, reduced skin hair, dependent rubor, and pallor on leg elevation. An ischemic foot may appear pink and relatively warm even with impaired perfusion due to arterio-venous shunting. Other signs suggestive of ischemia include claudication (pain in the leg muscles and usually exercise-induced), absence of peripheral pulsations, and a temperature difference between the feet[40]. A DFU is a complicated wound that poses a challenge to conventional wound dressings, whereby it demands advanced therapies to address the specific requirements for wound treatment management. Conventionally, the wound is managed with debridement of necrotic tissue and contaminants from the wound bed. Then, a physical dressing is put in place to prevent the wound from drying out while preventing further contamination to the wound bed. However, debridement does not affect surface bacterial counts and it is also not ideal as a treatment. Ultimately, both wound debridement and wound dressing aim to create an optimal environment for the wound to heal[41].

It has been widely demonstrated the effect of FIDIA HYALURONIC ACID 200kDa on improving the complete healing rate of diabetic foot.

Four studies that evaluated the rate of healing of diabetic foot that were treated with HA or standard therapy. The meta-analysis performed indicated that HA has significant benefit for increasing the healing rate of these ulcers over standard treatments. ***Indeed, the meta-analysis proposed by Chen et al. 2014, confirmed the finding that HA is beneficial in treating diabetes wound ulcers by increasing the rate of wound healing. It also showed HA is beneficial, independent of the form in which the compound is applied to the wound[42].***

In order to confirm the efficacy of HA in the management of metabolic ulcers, several studies have been conducted using ***FIDIA HYALURONIC ACID 200kDa*** *0.2 % and* ***all the studies confirmed the efficacy of FIDIA HYALURONIC ACID 200kDa 0.2%, demonstrating considerable benefits compare with other therapies usually carried out in the treatment of poorly healing skin wounds of vascular origin[43,44,45, 46].***

Furthermore, the studies performed underlined the easy application of FIDIA HYALURONIC ACID 200kDa 0.2% and in particular the safety profile, since it was well tolerated by treated patients, without generating any local or general adverse reactions[44].

Compared to the control group, presenting same type of lesion, in patient treated with FIDIA HYALURONIC ACID 200kDa 0.2%, the re-epithelization time has been demonstrated to be faster[47,48].

Additionally, in patients with sluggish ulcers due to vascular insufficiency, in comparison with a group treated with conventional therapy were evaluated by means of a daily index of epithelization, appearance of ulcer ground and edges. ***An earlier epithelization of ulcer due to vascular causes was evident, which confirmed that the exogenous supply of hyaluronic acid represents a more effective therapy than the conventional therapies usually applied in control patients[49].***

Moreover, in extreme cases, venous leg ulcers can remain indolent and unresolved for long periods of up to years. Tagliagambe et al. described the case of a patient with closure of a recalcitrant VLUs, most likely caused by venous insufficiency, treated initially with debridement and compression therapy for 16 weeks, and then treated with FIDIA HYALURONIC ACID 200kDa 0.2%.

After the initiation of the FIDIA HYALURONIC ACID 200kDa therapy, the patient achieved complete wound closure in four weeks of treatment.

This result suggests that further studies should assess the role of HA sodium salt 0.2% in the management of VLUs[50].

Another multicenter clinical trial involving 100 patients with venous leg ulcers demonstrated the efficacy and safety of the association of collagenase and hyaluronic acid during the preparation phase. The biological synergy between collagenase and FIDIA HYALURONIC ACID 200kDa provides one of the best approaches, since the beginning of the treatment, showing a clear

effect of HA in promoting the natural healing process. ***In the same clinical trial, all the other parameters evaluated (odor, erythema, tissue viability and moisture balance) showed a significant improvement over time. Importantly, the safety of FIDIA HYALURONIC ACID 200kDa was confirmed being globally satisfactory[51].***

Besides, a clinical study performed by Rueda Lopez (2005), in different type of wounds (Diabetic foot, Venous Ulcers, Vascular Ulcers) demonstrated a great efficacy of FIDIA HYALURONIC ACID 200kDa 0.2%. *The authors highlight the results in terms of healing, and the improvement of the wound. In addition, 80% of the wounds healed in less then 11 weeks, with no adverse reactions or side effects. Despite their complexity, in diabetic foot lesions, those of vascular aetiology and pressure ulcers, the application of FIDIA HYALURONIC ACID 200kDa 0.2% seems to be a good alternative treatment given the results obtained (cicatrization of 71.4% of this type of lesion). Reducing the treatment time and the number of treatments, according to the results obtained in the present study, means decreased procedure costs and improved quality of life in people with cutaneous lesions[52].*

It is possible to consider that a topical treatment with HA 0.2% is well tolerated by patients and gives a low allergy index compared to other therapeutical approaches. The reduced recovery time must be considered excellent, also in terms of costs and good tolerability. Costs include in the same number medication expenses, in relatively moderate times contained, and quick functional recovery of patient, that allows a social expense reduction[53].

DERMATITIS

Facial seborrheic dermatitis is a very common presenting problem in dermatology patients[55]. The condition most commonly occurs in infants within the first three months of life and in adults between 36 and 60 years if age. In adolescents and adults, it usually presents as scalp scaling (dandruff) or as mild to marked erythema of the nasolabial fold during times of stress or sleep deprivation. The latter type tends to affect men more often than women and often is precipitated by emotional stress. An uncommon generalized form in infants may be linked to immunodeficiencies. Despite the high prevalence of seborrheic dermatitis, little is known about its etiology. However, several factors (e.g. hormone levels, fungal infections, nutritional deficits, neurogenic factors) are associated with the condition. The possible hormonal link may explain why the condition appears in infancy, disappear spontaneously, then reappears more prominently after puberty[54]. The papulosquamous disorder is usually found on the scalp, face, or trunk, all of which are sebum-rich areas.

Effective therapies for seborrheic dermatitis include anti-inflammatory (immunomodulatory) agents, keratolytic agents, antifungals, and alternative medications (as Tea Tree Oil)[54].

One clinical study has been performed in order to evaluate efficacy and safety of FIDIA HYALURONIC ACID 200kDa in the management of mild-to moderate facial seborrheic dermatitis. The area to be treated was gently cleansed and then a thin layer of product was applied twice a day.

A significant improvement was achieved after 4 weeks of treatment in scale, erythema and pruritus. At weeks 8, after 4 weeks from disruption of treatment with the gel, parameters continued to improve and the provider global assessment

(PGA) resulted ameliorated from baseline in 92.3% of subjects. FIDIA HYALURONIC ACID 200kDa was applied twice daily, in the morning and evening. Treatment was continued for four weeks. Tolerability of the hyaluronic acid sodium salt gel 0.2% was excellent since no subjects experienced any adverse events[55].

The same authors evaluated the efficacy and safety of of FIDIA HYALURONIC ACID 200kDa in the management of ***Rosacea*** *which is a chronic cutaneous disorder characterized by flushing, erythema, telangiectasia, edema, papules and pustules. The cause of this inflammatory disorder is unknown but is thought to be multifaceted. Primary treatments for rosacea are typically oral antibiotics and topical therapies.* ***The authors demonstrated a clear reduction in papules, erythema, burning or stinging, and dryness at 4 weeks. At week 8, the global assessment was improved in almost all patients (78.5%). Also, in these patients compliance and tolerance were excellent***[56].

OTHER CLINICAL CONDITIONS

Hyaluronic Acid (HA) has been predominantly employed in wound healing due to its physiological action in support the healing process. Additionally, HA can be used also in other skin clinical conditions, as **actinic elastosis**, which occurs predominantly in chronically sun-exposed skin areas such as the temples, forehead and nape of the neck and appears histologically as a degeneration of the elastic fibers in the corium. The actinic elastosis is a chronic alteration of the corial connective tissue which is caused by ultraviolet and infrared radiation and which manifests itself in older age. The skin appears marbled in colour, scaly and above wrinkled.

Altmeyer (1992) evaluated the efficacy and safety of hyaluronic acid in the treatment of actinic elastosis. The study evaluated 30 patients for a period of 6 months. Hyaluronic acid was applied to the face and lightly massaged. ***The treatment with HA led to an improvement of symptomatology demonstrating its efficacy and safety***[57].

HYALURONIC ACID VERSUS OTHER TREATMENTS

Several clinical studies have been performed in order to evaluate the efficacy and safety of HA in the management of acute and chronic wounds compared to other therapeutical approaches. As previously described, HA has been widely used in the management of wounds ***demonstrating a significant effect in improving re-epithelization and reduction of ulcer dimension compared to low frequency pulsed electromagnetic field***[22] ***or to non-adhesive paraffine gauze-pads***[21].

Furthermore, compared to other substances used to manage wounds and specifically burns, as Triticum Vulgaris, HA demonstrated to be more efficient, and above all to rapidly improve wound healing[58].

In addition, Torregrossa et al. evaluated the efficacy of HA versus therapeutic topic protections (e.g. paraffinate gauze pads). The study results highlighted an earlier epithelization of the ulcer in the HA-treated patients showing that the exogenous supply of HA represents a more effective therapy than the conventional measures in control patients[49].

HYALURONIC ACID COMBINED WITH OTHER SUBSTANCES

HA can be also found in different formulation in combination with other substances already known and applied in the management of wounds.

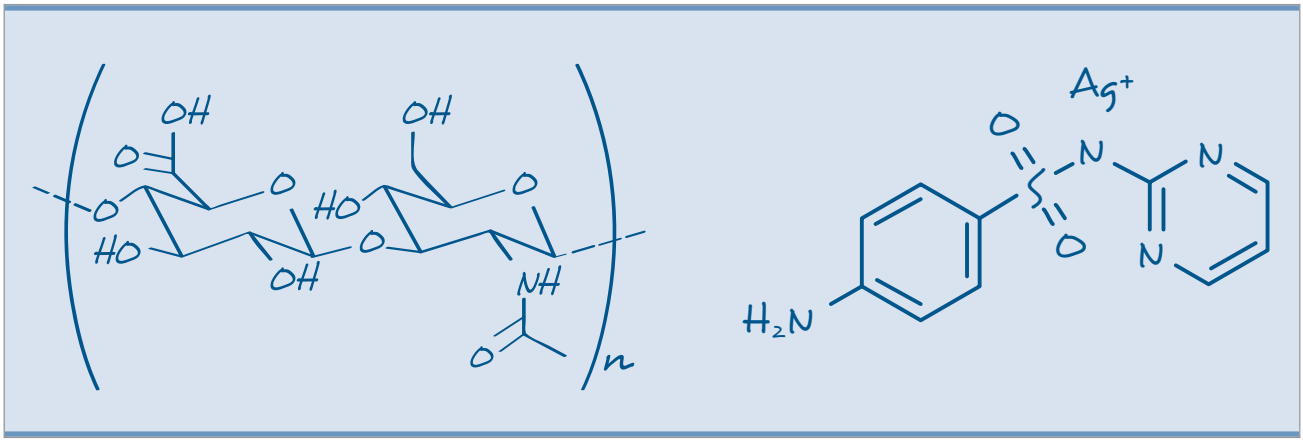
HYALURONIC ACID (HA) + SILVER SULFADIAZINE (SSD)

Sulfadiazine exerts a bacteriostatic effect by acting on the cell membranes of microorganisms, while silver nitrate exerts its effect on the endocellular structures. Since both Hyaluronic Acid (HA) and Silver Sulfadiazine (SSD) were used in therapy for decades and their efficacy is well documented, a topical treatment combining these two agents was formulated and studied in 2005 by Costagliola & Agrosi[32].

This multinational, multicenter, randomized, double-blind, controlled, parallel-group study compared a fixed combination cream containing FIDIA HYALURONIC ACID 200KdA 0.2% and silver sulfadiazine 1.0% (HA-SSD) versus a 1.0% silver sulfadiazine cream (SSD) alone. A total of 111 adult patients with a superficial second-degree and deep second-degree burns, were randomized to receive HA-SSD or SSD alone. Treatments (approximately 5g/100 cm2) were applied once a day until the wounds healed, but for no longer than 4 weeks. The results obtained showed that both the fixed combination HA-SSD and SSD alone, were effective and well tolerated topical agents for the treatment of second-degree burns. All burns were healed except in one patient treated with SSD.

Importantly, it was observed that HA-SSD caused significantly more rapid healing than SSD alone.

Both treatments were well tolerated: only one patient in the SSD group showed adverse events (shivering, fever, and headache), whose relationship with the drug were judged as possible. The combination promoted significantly faster healing of the burns compared to SSD alone and thus may enrich the assortment of topical medications available for the treatments of burns[32]. ***These results have been confirmed also by a study performed by Koller J et al. showing how the combination HA and SSD significantly reduced healing time and indirectly improved local edema occurring shortly after injury***[59]***. Furthermore, the early re-epithelization was also confirmed by Peghetti A et al. in patients treated with the combination of HA and SSD***[23]***.***

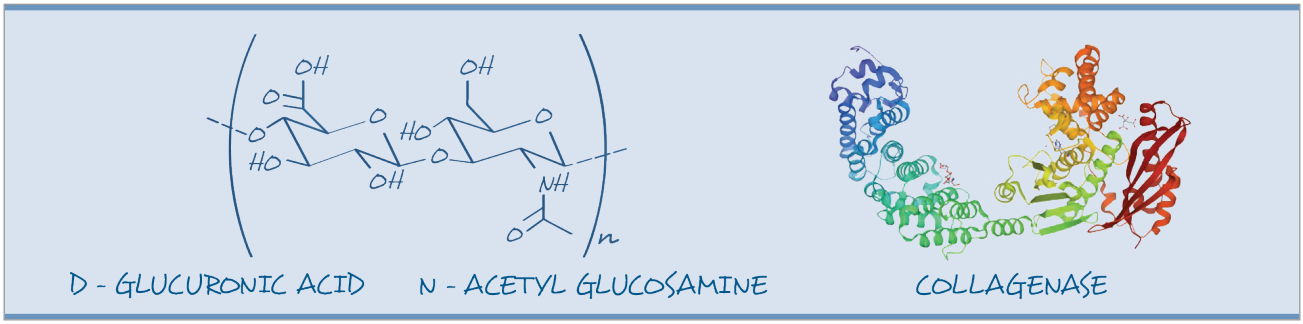


COLLAGENASE (FROM VIBRIO ALGINOLYTICUS STRAIN)

Beside SSD, FIDIA HYALURONIC 200kDa 0,2% has been also combined with collagenase.

The combination has been demonstrated to significantly decrease the pain felt by the patient, allowing the healing of the wound, thus improving in a non-negligible way his quality of life[60]***.***

In addition, the application of this combination generates a microenvironment which promote the natural healing process. Therefore, by a passive mechanism, HA permits the tissue hydration, contributes to the osmotic balance, and stabilizes the ECM structure[62].

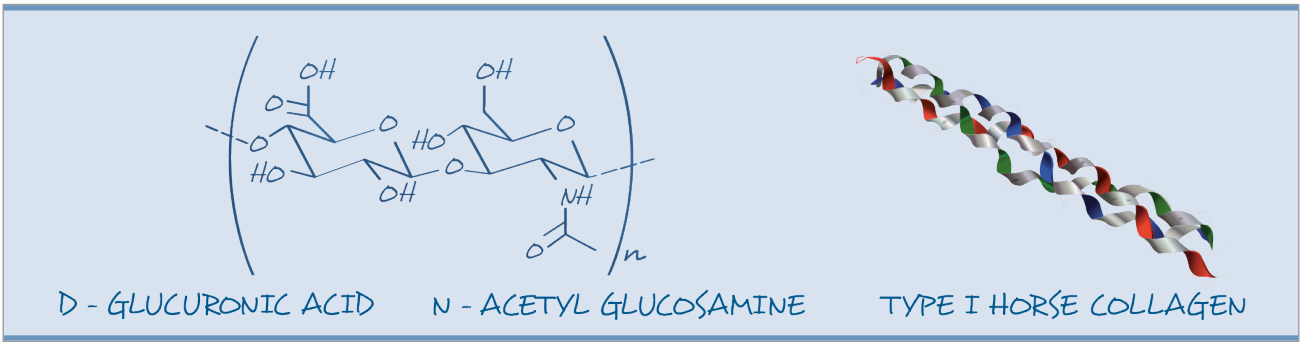


HYALURONIC ACID (HA) + TYPE I HORSE COLLAGEN

Furthermore, HA can be associated also to type I horse collagen and largely used in the management of wounds.

A clinical experience has been reported by Torresetti et al which evaluated this combination in patients with cutaneous open wounds, including venous ulcers, posttraumatic wounds, surgical wounds, pressure sores, burns, peristomal ulcerations and skin ulceration after radiotherapy. The average healing time was 31 days. The potential of HA in controlling tissue hydration, ensured a moist wound bed that is fundamental for a correct reparative process[63].

Additionally, Caravaggi et al. conducted a pilot study on a pad containing FIDIA HYALURONIC ACID 200kDa + type I horse collagen on 38 consecutive diabetic foot patients (dorsal and plantar), free from distal vascularization defects and from local and systemic signs of infection. The treatment protocol was based on surgical debridement, followed by cleansing with physiological solution and the application of the pad of HA+Collagen, finally covered by greasy gauzes. The study showed a high percentage of healing of both dorsal and plantar ulcerative lesions in a short treatment period when compared with the literature data. Analyzing the plantar neuropathic ulcerative lesions treated with TCC, a 100% complete healing rate was observed at week 13rd compared to 56% at 12th week reported in the literature from controlled clinical trials. The total healing rate (46%) and the reduction in ulcer area (78%) at week 12 are also encouraging compared to the data reported in the literature. During the whole observation period, no side effects or infections of the treated wounds were observed[64].



Published clinical evidence for FIDIA hyaluronic acid 200 kda

Study title / Authors	N. patients	Clinical condition/pathology	Treatment	Clinical benefit
ACUTE WOUNDS				
A controlled study on the therapeutic efficacy and tolerability of Bionect Gause-pads (labelled CNT/S) in the treatment of second-degree burns. **Pellerano S.** 1987. Clinical study Report CN/769	30	Second-degree burns	HA vs Triticum vulgaris	• More efficient and more rapid than the control Triticum vulgaris • Faster favorable results and a "restitutio ad integrum" of the lesioned area • Lower duration of treatment • Excellent tolerability
Clinical observation on the use of hyaluronic acid in dermatology. **Venturini D.** Giornale Italiano di Dermatologia. 1985; 120: 1-6	38	Accidental burning	HA	• Faster formation of granulation tissue which consequently resulted in surface re-epithelization • HA favors granulation processes up to complete epithelium recovery • Time needed for re-epithelization, it was possible to observe: ✓ 8.71 days with variations from 4 days minimum to 14 days maximum for 1st and 2nd degree burns ✓ 9.00 days with variations from 3 days minimum to 15 days maximum for 2nd degree burns ✓ 18.06 days with variations from 11 days minimum to 30 days maximum for 2nd and 3rd degree burns
Clinical study of the specialty Bionect Gauze in burns. **Bonfacini V.** 1987. Clinical Study Report CN/768	60	First-, second- and third-degree superficial and deep burns	HA vs Triticum vulgaris	• High rapidity in the formation of the granulation tissue • Better efficacy that the standard, both on the symptomatology as well as on the objective signs, carrying out anti-flogistic, and anti-exudative actions and a stimulatory action on the mesenchymal repair processes therefore re-epithelization • Remission of the symptomatology observed starting from the 7th day of therapy • Marked reduction in the burn diameter
Role of a HA -based Hyaluronic Acid in re-epithelization: a clinical model. **Soma PF**, Stella M, Comitini S. 1988. 37° National Meeting of the Italian Society of Plastic, Reconstructive, and Aesthetic Surgery.	40	Burns	HA vs standard care	• Significant faster re-epithelization compared to controls
Hyaluronic acid effects on deep burns healing. **Siliprandi L**, Casadei A, Avventi E, Chiarelli A. Riv. Ital. Chir. Plastica. 1987; 19: 635-644	9	Burns	HA vs standard care	• Better enhancement of neovascularization • Better development of granulation tissue • Homogenous lesion • Better appearance (better cleansing than the control)

Study title / Authors	N. patients	Clinical condition/pathology	Treatment	Clinical benefit
Controlled clinical study of the therapeutic efficacy on the topical application of medicated gauzes containing the sodium salt of hyaluronic acid (Bionect Gauze) in the treatment of Second-degree burns. **Carcano F.** Clinical Study Report. 1987. CN/766	60	Second-degree deep and superficial burns	HA vs Triticum vulgaris	• Good therapeutic efficacy, promoting complete re-epithelization of the lesion and the disappearance of oedema and pain; • Produce better healing of the lesion compared to controls • Great tolerabilty
Clinical application of BIONECT (Hyaluronic Acid Sodium salt) in wound care by cesarean section and episiotomy. **Ivanov ST**, Mihova M, Ruseva R, Batshki I. Akush Ginekol (Sofiia). 2007; 46 Suppl 4: 20-6.	47	Surgical wounds (Cesarean section and episiotomy)	HA vs standard care	• Must faster management of oedema, exudation, infiltration, superficial blood collections in patients treated with HA • Reduction of local signs of inflammation
Hyaluronic acid in the treatment of acute and chronic wounds. **Slonkova V**, Vasku V, Jedlickova H. Hojení ran. 2010; 4 (1): 4-8	20	Surgical wounds	HA	• Improvement of healing • Quick pain relief • Quality of life improvement
A placebo-controlled, randomised, double-blind study on the efficacy and safety of hyaluronic acid cream in wound healing after criosurgery of a basalioma. Clinical study report Y5-3-89-38	60	Surgical Wounds	HA vs placebo	• Markedly reduced duration of healing process in comparison to placebo • Healing, wound surface
Observations on the comparative use of hyaluronic acid sodium salt and triticum vulgaris extract in 20 subjects affected by ulcers of different etiology. **Bruno RN.** 1983. Clinical Study Report Cn/259.	20	Ulcers of various origin	HA vs Triticum Vulgaris	• Completely recovery in patients treated with HA • Remarkable reduction of ulcerated area and lively granulation • HA present considerable benefits compared with other therapies usually carried out in the treatment of poorly healing skin wounds
Hyaluronic acid in the healing processes of skin ulcers. **Retanda G.** Giorn. It. Derm. Vener. 1985; 120: 1-5	20	Ulcers of different origin	HA	• Hyaluronic acid support cicatrization of slow-healing wounds
CHRONIC WOUNDS				
The biological rationale underlying the therapeutic effectiveness of exogenous hyaluronic acid and low-frequency pulsed electromagnetic fields in pressure ulcer medical treatment. **Vannini AM**, Ferrari MP, Dalla Valle I, Magnolfi G, Perbellini A, Rastrelli A, Govoni E. Cutaneous Development, Aging and Repair; 1989; 18: 81-95	20	Pressure sores	HA vs PEMF (low frequency pulsed electromagnetic fields)	• Reduction of the ulcer dimension • Improvement of ulcer healing was observed during the 30 days of follow up
The effect of local applications of hyaluronic acid associated with laser therapy in the treatment of pressure sores. An open-label, controlled clinical trial. **Tarantola P**, Lombardi G, Inzoli MR, Malgeri C, Magnolfi G. Giorn. Gerontol. 1990; 38: 151-155	25	Pressure sores	HA vs non-adhesive paraffine gauze-pads	• Superiority of hyaluronic acid treatment • Complete re-epithelization of half the lesions • Remarkably dimension reduction and seriousness of the remaining lesions.

Study title / Authors	N. patients	Clinical condition/pathology	Treatment	Clinical benefit
Alternative methods in the treatment of varicose ulcers and results. **Lapilli A**, Alonzo R, Zendron R, Piccinni L. Minerva Stomatologica. 1986; 34 (4): 251-254	30	Varicose Ulcers	HA vs standard cleasing or elastic bandage	• Better cicatrization progress in patients treated with HA compared to those treatment
Clinical trial with hyaluronic acid in the therapy of leg ulcers. **Raffanelli A**, Zinna G. 1986. Clinical Study report CN/410	40	Ulcers	HA vs Choramphenicol (CAF)-collagenase	• Hyaluronic acid favours a rapid cleaning of the fundus with removal of exudative tissues and a less rapid, but even good normalization, of edges
Effects of hyaluronic acid on ulcers wound healing: a comparative study. **Passarini B**, Tosti A, Fanti PA; Varotti C. Giorn It Derm Vener. 1982; 117	48	Ulcers from venous stasis	HA vs other therapeutical approaches (e.g. hydroxyproline, local antibiotics, proteolytic agents)	• HA improves re-epithelization, ground and margin appearance • HA treatment was more efficient than conventional therapy
Clinical trial of the topical use of hyaluronic acid-soaked gauzes in the treatment of sluggish ulcers. **Torregrossa F**, Caroti A. Giorn It Derm Vener. 1983;118	47	Vascular and post-traumatic ulcers	HA vs control (other therapeutical topical approaches)	• HA improves re-epithelization, ground and margin appearance • Earlier epithelization of the ulcer was evident in the HA treated group • HA was a more effective therapy than conventional measures
Hyaluronic Acid Sodium Salt 0.2 % Gel in the treatment of a recalcitrant distal leg ulcer: a case report. **Tagliagambe M**, Elstrom TA, Ward DB. J Clin Aesthet Dermatol. 2017; 10 (11): 49-51	1	Venous leg ulcer	HA	• HA treatment allowed to complete wound closure in four weeks of treatment • HA is safe, efficacious, expeditious and a cost-effective option for the treatment of recalcitrant ulcers
MANAGEMENT OF CUTANEOUS IRRITATIONS AND LESIONS				
Efficacy and safety of a low molecular weight hyaluronic acid topical gel in the treatment of facial seborrheic dermatitis final report. Schlesinger T, Powell CR. J Clin Aesthet Dermatol. 2014;7(5):15–18	18	Facial Seborrheic dermatitis	HA	• Improvement in all parameters measured (erythema, pruritus
Efficacy and tolerability of low molecular weight hyaluronic acid sodium salt 0.2% cream in rosacea. Schlesinger TE, Rowland Powell C. J Drugs Dermatol. 2013; 12 (6): 664-667	14	Rosacea	HA	• Improvement in all parameters evaluated (papules, pustules, erythema, edema, telangiectasia, burning, stinging, dryness
Sonographic investigation of efficacy of Hyaluronic acid cream in actinic elastosis. A pilot study. Altmeyer P. 1992. Clinical Study Report Y5-3-90-46	30	Actinic Elastosis	HA	• HA led to an improvement of symptomatology demonstrating its efficacy and safety

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