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REVIEW

Properties and potentialities of hyaluronic acid and eXcellent Tridimensional Reticulation as a filling agent: a review

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Abstract

Cutaneous ageing has attracted widespread interest in recent decades, and the global market for non-invasive rejuvenation procedures is expanding, with hyaluronic acid (HA)-based fillers playing a significant role. The conversion of HA into a filler product is a complex and multidimensional process that involves several key stages. Each HA-based filler has rheological features that vary depending on the manufacturing process and lead to particular behaviours when injected into specific anatomical locations. Clinicians must be equipped to select dermal fillers with properties that align with the intended aesthetic outcome. Several key factors influence this decision, including the anatomical characteristics of the injection site, the consistency and thickness of the surrounding tissues, the firmness of retaining structures, the degree of mimetic muscle activity and external mechanical forces on the face as well as the specific anatomical plane targeted for injection. These variables differ not only by facial region but also between individuals, highlighting the importance of thorough patient evaluation. HA fillers are widely recognized for their safety and biocompatibility, with most adverse effects being localized and transient, typically occurring at or near the injection site. Our literature review covers the capabilities and potentials of HA and eXcellent Tridimensional Reticulation (XTR™) in the treatment of skin ageing.

Keywords: aesthetic outcomes, facial rejuvenation, filler, hyaluronic acid, XTR™ Technology.

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Introduction

With advancing skin ageing, both structural stability and functional integrity progressively decline. At the molecular scale, there is a reduction in reserve capacity and peak functional performance, whilst clinically, signs such as fine wrinkles, dryness, pallor and diminished elasticity, become increasingly evident (Table 1).[1–3]

Histologically, ageing skin demonstrates a thinning of the epidermis and progressive flattening of the dermal–epidermal junction, which contributes to increased skin fragility and impairs nutrient exchange across this interface.[1,4] The decrease in dermis thickness is accompanied by an overall reduction in vascularity and cellularity as well as in the number of fibroblasts and mast cells. Levels of hyaluronic acid (HA) and glycosaminoglycan in the dermis also decline, and the depletion of collagen and elastin leads to disorganization of connective tissue. Furthermore, the decrease in the interface area between epidermis and dermis may lead to a reduction in the mechanical stability of the two layers. These molecular changes contribute to the formation of wrinkles and loss of elasticity.[1,4]

At the muscular level, facial ageing is notably influenced by the progressive laxity of the cutaneous aponeurotic structures. Repetitive facial movements and muscle contractions contribute to the formation of wrinkles, which can be categorized as static (visible at rest and accentuated by movement) and dynamic (appearing in conjunction with muscle activity). Dynamic wrinkles often result from compensatory hypercontraction of facial muscles in response to age-related dermal thinning and atrophy.[5]

Photoageing is the most frequent type of ageing caused by environmental causes. Long-term exposure to sun

Table 1. Structural and functional changes of normal ageing skin.[3]

Skin component	Structural and functional changes
Epidermis	Thinner, with corneocytes less adherent to one another
Melanocytes and Langerhans cells	Decrease in number
Dermis	Atrophic, avascular and acellular
Subcutaneous tissue	Decrease in face, shins, hands and feet
Subcutaneous tissue	Increase in abdomen in men and thighs in women
Eccrine glands	Decrease in number
Sebaceous glands	Increase in size with lower secretory output
Nail plate	Thinned, with ridged and lustreless surface
Hair follicles	Reduced density per unit area on face and scalp

radiation can account for almost 80% of premature facial ageing. Roughness, deep wrinkles, dryness, loss of elasticity and uneven pigmentation are common clinical indicators of photoageing, and they are most visible on the neck, face and dorsal forearms. Elastosis, which causes amorphous elastin deposition directly below the dermal–epidermal junction, is the major feature of photoaged skin.[6]

Skin ageing can have a negative and considerable impact on quality of life, particularly for those who have dermatological conditions that require medical treatment. The most common patient request in aesthetic dermatology is the removal of unflattering expressions linked with facial and cutaneous ageing. Non-surgical interventions for facial ageing encompass both topical skin care products – commonly used in the early stages of ageing and representing the most accessible and widely adopted option[2] – and non-invasive aesthetic procedures, which are experiencing continuous global growth in popularity and demand. The last International Survey on Aesthetic/Cosmetic Procedures performed in 2023 showed a total increase of 6.5% in injectable procedures compared with the previous year.[7] Amongst them, botulinum toxin was the most popular non-surgical technique for both men and women as well as for all age categories, with 8.8 million procedures carried out by plastic surgeons worldwide. This was followed by 5.5 million procedures using HA, which represents a 29% rise compared with the previous year. Based on the data available in the survey, these treatments were performed prevalently on women (85.5%), located in the USA, Brazil, Germany, Turkey and Mexico.[7]

With the increasing popularity of non-invasive facial rejuvenation procedures, aesthetic practitioners must be informed about and comfortable working with soft tissue fillers. With the growing availability of dermal fillers, there is an increasing demand for a deeper understanding of their underlying properties. Since these products are not suited to every clinical indication, the selection of an appropriate filler depends largely on the practitioner's expertise and adherence to the manufacturer's specific instructions, including the intended anatomical plane of injection.[8]

Amongst fillers, the proprietary eXcellent Tridimensional Reticulation (XTR™) technology (Definisse™, RELIFE S.r.l., Florence, Italy) was recently introduced globally for use as HA-based fillers. XTR™ technology leads to the formation of HA fragments of specific size and with viscoelastic properties compatible to skin are cross-linked to produce a polymer that may be suitable for certain patient profiles.[9]

This review summarizes the most relevant novelties in the field of HA fillers, focusing on the properties and potentialities of HA and XTR™ in the treatment of skin ageing.

Methods

We performed a narrative review by searching PubMed for articles published between 2004 and 2024 using the terms "skin ageing", "aesthetic procedures", "hyaluronic acid" and "filler". The search was limited to studies related to human participants and available in English. Articles were reviewed and selected based on their relevance to the topic. Additionally, the reference list from the selected articles was manually selected to ensure comprehensive coverage.

Review

History of matrices

In the early 1900s, in Vienna, surgeons performed the first attempts at facial rejuvenation by injecting liquid paraffin; however, the occurrence of numerous complications halted this practice.[10] Subsequently, multiple synthetic fillers, such as silicone oil and polytetrafluoroethylene, were investigated and frequently used.[11,12] Silicone is not stable and may migrate towards other districts from the original implant and was prohibited in the 1990s following

the occurrence of severe side-effects, including allergies, inflammatory reactions and granulomatous reactions.[13]

In 1981, a significant advancement towards modern fillers was accomplished when the FDA approved the bovine collagen fillers Zyderm and Zyplast (Inamed, Santa Barbara, CA, USA) for cosmetic use.[14] Collagen is a component of the skin support, and it can be used to augment lip volume or ameliorate wrinkles as well as post-acne and traumatic scars. Bovine collagen proved successful in improving fine wrinkles; however, it frequently triggered allergic responses, requiring skin testing before use, and its effects were relatively short-lived.[15] These difficulties, combined with the increased concern of bovine spongiform encephalopathy, led to these injections only being administered to a limited subset of highly wealthy people.[15]

Continuous progress and research have led to the development of the modern fillers currently in use. The latest generation of fillers may be divided into two major groups: (1) permanent or non-biodegradable fillers and (2) biodegradable or absorbable fillers.

Permanent or semipermanent fillers are composed of microspheres of synthetic material that do not dissolve and remain in the body. The collagen component provides the first repair after injection into the deep derma, which degrades in 1–3 months. During this time, the permanent filler is encapsulated by connective tissue and determines the desired volume augmentation. However, over time, the weight and density of the material may cause it to slowly migrate from the injection site due to gravity. The permanent filler can only be removed surgically.[16] Examples of permanent fillers include poly(methyl methacrylate), which was approved by the FDA for the treatment of nasolabial folds,[15] and polyacrylamide gel-based products.

Biodegradable fillers contain polysaccharides, which are dermal components that gradually decrease in terms of concentration and production with ageing. They bridge the spaces between wrinkles and increase cutaneous hydration when exogenously injected. Following a filler injection beneath the skin, the body can absorb these molecules in several ways, either by desegregation or enzymatic digestion. The period for elimination has a direct impact on the duration of the treatment, and varies across individuals as determined by their lifestyle (smoking, alcohol consumption, excessive exposition to sunlight or sunlamps).[17]

The most common absorbable fillers contain HA. Fillers composed of HA combined with calcium hydroxyapatite are widely used in clinical practice. Following the absorption of the carrier gel within a few weeks after injection, hydroxyapatite induces neocollagenesis, with the microspheres functioning as scaffolds for the deposition of new collagen fibrils. Injectable calcium hydroxyapatite was approved by the FDA in 2006 as a filler for the augmentation of moderate to severe nasolabial folds.[15] Polylactic acid fillers have seen a rise in popularity. Polylactic acid is a biocompatible, lab-engineered, biodegradable thermoplastic aliphatic polyester that does not trigger immune reactions. Polylactic acid encourages endogenous natural collagen production and delivers a sustained filling effect lasting 10 months or more,[18,19] and is commonly applied on wide-gap wrinkles to redefine the facial borders, cheeks, hands or neck by increasing volume. Several treatment sessions are needed to restore optimal facial volume, and patients must be counselled about the progressively evident outcomes.[15] Last, glycolic acid, an α-hydroxy acid with exfoliating properties, can be used as a biodegradable filler to stimulate the production of new cells and eliminate wrinkles and scars.[16]

HA-based fillers

Biology and application of HA in aesthetic medicine

HA is a glycosaminoglycan disaccharide composed of N-acetyl-D-glucosamine and D-glucuronic acid units alternately linked via β-1.4 and β-1.3 glycosidic bonds. HA plays an important function in preserving skin hydration and volume due to its capacity to retain up to 1000 times its molecular weight in water, ensuring skin softness and elasticity.[20] Additionally, HA facilitates the proliferation and migration of fibroblasts, which produce collagen and elastin, and contributes to neutralizing reactive oxygen species, thus mitigating premature cutaneous ageing.[20]

As the body ages the amount of HA in the skin steadily decreases. HA levels stay reasonably steady until around the age of 20, after which they begin to fall. By the age of 55 years, the HA content in the skin is half of what it was at 35 years.[21] Injecting HA into the dermis of aged skin results in high water absorption and increased skin volume and compressive tension on surrounding fibroblasts, which induces fibroblasts to produce new collagen, thus increasing the dermis volume and subcutaneous tissue. HA is degraded by hyaluronidase in the body, with a half-life of approximately day and complete turnover within 1 week. HA fillers improve the physical and rheological properties of natural HA to slow down its degradation.[21]

Manufacturing procedure

Both animal-derived and bacteria-derived HA share the same fundamental repeating disaccharide structure,

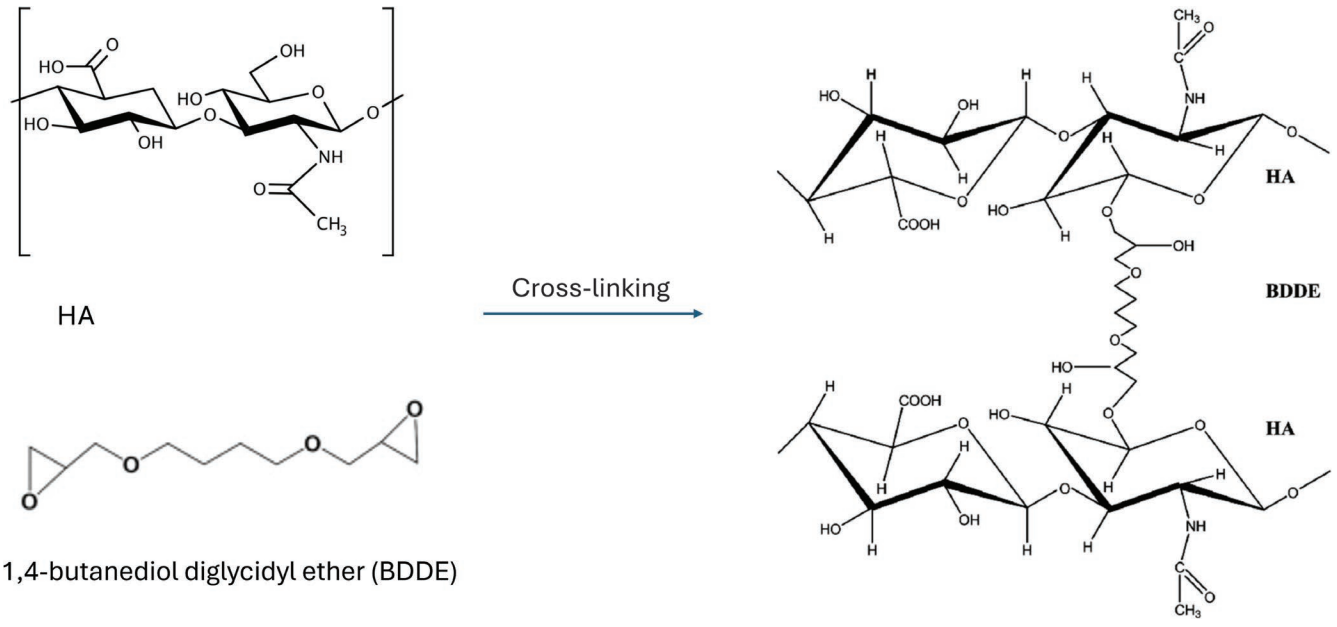
making either source suitable for use in dermal fillers. However, bacterial fermentation has become the preferred method of production due to its ability to yield HA with greater purity, batch-to-batch consistency, and a lower risk of triggering allergic responses compared with animal-derived alternatives.[21]

HA sodium salt is the basic ingredient used in HA fillers and is usually delivered in a powder form. Its quality is critical in the development of premium fillers because using high-grade HA greatly minimizes the risk of undesirable effects. HA naturally consists of lengthy molecular chains that hold significant moisture; nevertheless, their vast size inhibits their ability to permeate the skin efficiently. Therefore, to improve absorption through the skin's stratum corneum, the molecular weight of HA must be reduced to obtain medium-molecular-weight HA (2.5–3.2 million Dalton), which provides a reasonable balance between moisture retention and barrier protection. Although microbial-derived HA typically varies from 50 to 60 million Dalton, additional purification is required for medicinal uses, especially injectables, to produce HA powders with molecular weights ranging from 50 to 3 million Dalton.[21]

Free HA, like natural HA, is rapidly destroyed by hyaluronidase after injection, disappearing within a few days.[21] Therefore, cross-linking of HA molecules is necessary to improve their stability and transform them into a long-lasting filler that can retain volume. The two main approaches to HA cross-linking in filler production are physical and chemical techniques. Physical cross-linking involves the creation of bonds between HA chains through non-covalent interactions without altering the chemical structure. Chemical cross-linking entails the use of cross-linking agents to form covalent bonds between polymer chains. Precise control over the degree of cross-linking can be achieved by adjusting the amount of cross-linker used, regardless of the density or arrangement of HA chains. Commonly used cross-linkers include 1,4-butanediol diglycidyl ether, divinyl sulfone, bis-epoxides and polyethylene glycol, all of which have established safety profiles and low toxicity. Currently, nearly all HA fillers use 1,4-butanediol diglycidyl ether as the major cross-linking agent (Figure 1).[21]

Biphasic and monophasic fillers have diverse physical properties due to the different cross-linking procedures and the molecules inside the gel matrix. Biphasic fillers are normally produced with low concentrations, usually 1–3%, of cross-linking agent. Cross-linking conditions in terms of temperature, stirring speed and reaction time are carefully controlled to achieve a cohesive and resistant gel. This mass is then divided into smaller granules, which confer the peculiar gritty texture. On the other hand, monophasic fillers, in which the gel matrix is based on cross-linked HA only, are created through a chemical cross-linking procedure in which the degree of cross-linking is directly proportional to the concentration of cross-linker used, influencing the number of HA molecules involved. This approach produces a gel mass that is often softer and more malleable, frequently having a slightly sticky sensation when touched.[21] The gels are then transferred into syringes, packaged and sterilized to prevent contamination.[21]

Figure 1. Cross-linking of hyaluronic acid with 1,4-butanediol diglycidyl ether.



HA, hyaluronic acid.

Rheological properties

The viscoelastic characteristics of HA fillers are described using five main rheological parameters: the elastic/storage modulus (G′), the viscous/loss modulus (G″), the complex modulus (G*), tangential delta (tan δ = G″/G′) and complex viscosity (η*). The elastic modulus (G′) is a measure of the energy stored in a material on which shear deformation has been imposed. All HA fillers have a G′ > G″, which leads to a gel-like structure with the behaviour of a viscoelastic solid material. G* measures the total energy required to deform a material using shear stress, describing the global resistance to deformation of a material, independently of whether that deformation can be recovered (elastic) or not (viscous); a filler with high G* is more appropriate for implants in the deep anatomical planes, such as the supraperiosteal layer and deep-fat compartments. The ratio of these components (G″/G′) gives tan δ, which determines the solid (i.e. more jelly-like) or liquid-like behaviour (i.e. honey-like) of a material.[9] cross-linking, molecular weight and the manufacturing process affect the rheological properties of HA fillers.

Understanding the rheological features of HA fillers is crucial for maximizing their clinical application. A filler with a greater elastic modulus G′ is more resistant to deformation, better retains its shape under pressure and is excellent for enhancing cheek volume; fillers with a lower elastic modulus are softer and more fluid, making them suitable for fine lines and wrinkles. Users must be aware of the exact production methods underlying the fillers they use because these processes considerably influence the consistency and performance differences between various types of fillers.[21]

The rheological properties of HA fillers can also be affected by additives required for pain management, for example, lidocaine.[9] Pain management is a crucial but often ignored factor of effectiveness in soft tissue filler injections. Preventive pain control not only alleviates discomfort but also reduces operational downtime and increases patient satisfaction. The use of lidocaine has resulted in a significant pain decrease during and after injections.[9] Additionally, the antihistamine properties of lidocaine help to minimize erythema, bruising and swelling.[9]

Comparison of properties of HA-based fillers

As described earlier, the degree of cross-linking and the additives present in HA fillers greatly affect their properties, and these need to be carefully assessed prior to their use. As an example, herein, we explore the molecular intricacies of XTR™ Technology and the differences amongst three Definisse™ HA fillers, produced through the XTR™ Technology, to better explain how cross-linking and rheological features can differentiate products (Table 2).

The Definisse™ touch filler (also available as Definisse™ touch with lidocaine) has a balanced distribution of cross-linking and molecular weight of HA chains, which determines its viscoelastic properties, characterized by an optimal G′ and balanced G″ values to be injected into the lips and nasolabial folds (Figure 2).[22] It is formulated with a low degree of cross-linking, optimizing flexibility and precision, which allows for seamless adaptation to facial contours and ensures natural results, particularly in areas requiring soft and delicate adjustments.

Definisse™ restore (also available as Definisse™ restore with lidocaine) features medium cohesivity and balanced viscoelastic properties, enabling controlled injection and uniform tissue distribution. Its rheological profile, highlighted by an optimal tan δ value, supports fluidity and elasticity. This formulation achieves a balance between structural integrity and adaptability, making it suitable for various facial augmentation applications.[23]

Definisse™ core (also available as Definisse™ core with lidocaine) leverages advanced rheological properties for enhanced volumization and stability. With a G′ of approximately 427 Pa at 0.7 Hz, a loss modulus (G″) of 26.9, tan δ of 0.063 and high cohesivity, it provides long-lasting results and resistance to deformation. These characteristics make it ideal for applications requiring structural support and durable contouring.[24]

Table 2. Comparison of rheological characteristics of hyaluronic acid fillers Definisse™.[22–24]

	G′ – 30°C at 0.7 Hz	G″ – 30°C at 0.7 Hz	tan δ	Level of cross-linking	Viscoelastic properties
Definisse™ touch	153.58	26.67	0.174	Low	High fluidity and low elasticity
Definisse™ restore	292.37	27.86	0.095	Moderate	Medium fluidity and medium elasticity
Definisse™ core	426.76	26.87	0.063	High	Low fluidity and high elasticity

Figure 2. Characteristics of Definisse™ fillers.[22–24]

	HA CONCENTRATION/ LEVEL OF CROSS-LINKING	NEEDLES	SYRINGES PER PACK	LAYERS OF INJECTION
DEFINISSE™ TOUCH FILLER + LIDOCAINE	HA: 23 mg/ml Level of gross-linking	2 X 27G 1/2″ thin wall Terumo	1 ml glass syringe	Mid to deep dermis and submucosa
DEFINISSE™ RESTORE FILLER + LIDOCAINE	HA: 23 mg/ml Level of gross-linking	2 X 27G 1/2″ thin wall Terumo	1 ml glass syringe	Deep dermis or subcutis
DEFINISSE™ CORE FILLER + LIDOCAINE	HA: 25 mg/ml Level of gross-linking	2 X 27G 1/2″ thin wall Terumo	1 ml glass syringe	Deep subcutis and/or supraperiosteal injection

HA, hyaluronic acid.

Fillers manufactured via XTR™ Technology have a relatively higher G′ than other HA fillers with the same indications, believed to have lasting effects and more pronounced lifting capacity.[8] By dissecting the scientific rationale behind each product, it is possible to grasp how the range addresses clinician and patient needs, harnessing the full potential of XTR™ Technology.

How to choose the right filler for each intervention

The rheological properties of the HA filler regulate its integration with the surrounding soft tissue and determine its ability to change the volume of the injected anatomical layer. Clinicians must be able to select fillers with the proper features to obtain the desired final clinical results.

The following factors drive the choice of filler: the anatomy of the injection site, consistency and thickness of tissues, firmness of the retention areas, strength of mimetic muscular activity and external pressures on the face and anatomical layer to inject. All these characteristics change in each facial location, necessitating an appropriate assessment when selecting a filler.[8]

Definisse™ touch filler, with a lower level of cross-linking, softer feel and lower G′ modulus, can adapt more easily to facial contours and provide subtle enhancements.[22] Whilst offering a low resistance to applied force, it still provides adequate tissue support and natural-looking results, particularly suitable for treating lips, nasolabial folds and first-time patients looking for subtle outcomes. Featuring a medium level of cross-linking, Definisse™ restore filler strikes a balance between stiffness and flexibility, as reflected in its moderate G′ modulus.[23] Definisse™ core filler, with its high level of cross-linking, delivers reliable tissue support and lifting effects, making it suitable for addressing moderate to severe volume deficits across various facial regions. Its notably high G′ modulus reflects significant resistance to applied forces, enabling precise tissue augmentation and structural stability. This combination allows clinicians to achieve enhanced volume and defined contours with precision and control, making it an effective choice for a broad spectrum of facial sculpting needs.[24]

Additionally, the balanced combination between G′ and G″, mirrored in the tan δ values across the Definisse™ fillers, ensures optimal spreadability and tissue integration, facilitating smooth injection and uniform distribution within the target area. This enhances the overall treatment experience for both injectors and patients, which can contribute to natural-looking results and patient satisfaction.

Clinical trials and real-world experience of Definisse™ fillers

Many advances have been made in the application of HA fillers and some clinical trials still ongoing to further investigate novel approaches.[25] Here, we report data from studies investigating the XTR™ technology applications.

A prospective, non-comparative, single-centre, phase IV trial to determine the efficacy of Definisse™ core with lidocaine filler in ameliorating skin quality and tissue volume in women with midface volume loss was conducted.[26] In the interim analysis 6 months after the injection, Definisse™ core with lidocaine significantly improved midface

volume deficits, skin quality and thickness. Injector and patient satisfaction with the therapy were reported, and only mild to moderate adverse events were described. These favourable outcomes in terms of skin quality, thickness and volumization persisted 12 months after the first injection. All patients described an aesthetic improvement at all time points based on the investigator-assessed Global Aesthetic Improvement Scale Assessment. Objective assessments using the 3D LifeViz technology validated the positive outcomes: the total cheekbone volume grew considerably to 12.4 mL. All participants agreed that the treatment was effective, that they were satisfied with the outcome and considered it natural-looking.[27] An 18-month follow-up was also analysed to assess the duration of clinical effects and tolerability.

A real-world study including 20 participants treated with an HA filler based on XTR™ technology (Definisse™ core filler + lidocaine by RELIFE) for midface restoration showed that the Global Aesthetic Improvement Scale Assessment and patient satisfaction were high 1 month and 3 months after treatment and most stated that they would receive the treatment again, thus supporting the effectiveness of the treatment in reshaping the curves of the zygomatic area.[28]

Safety of HA fillers

Safety and tolerability of HA fillers are well known, with most adverse responses occurring near the injection site. In the phase IV trial mentioned above, these reactions were low-grade (mild or moderate) and consisted of temporary pain/tenderness, lumps/bumps, skin redness, induration, oedema and bruising/haematoma, as well as colouring.[26,27]

In addition to early-onset reactions, such as allergic or hypersensitivity type I reactions, which occur within minutes to hours of treatment and are characterized by an immediate immune response mediated by immunoglobulin E antibodies, late-onset reactions (or delayed inflammation reactions) can occur and are probably mediated by T cells.[29–31] Late-onset reactions often appear weeks to months after HA filler injections, with a peak prevalence between 3 and 4 months. Foreign body granulomas, oedema, abscesses, post-inflammatory hyperpigmentation, nodules (inflammatory and non-inflammatory) and late bacterial infections are some of the clinical symptoms of these reactions.[29–31]

Understanding the risk factors for late-onset reactions is essential for reducing the occurrence of late-onset reactions in individuals who receive filler treatments. Risk factors can be related to the patient, the product or the procedure.[31] The patient's medical history, including medication, filler and procedure history as well as illnesses, health issues and allergies (for example, bee sting allergies), influences the likelihood of late-onset responses. Risk factors associated with product-related procedures are mainly due to the presence of impurities from cross-linking and fermentation. These components may determine inflammatory reactions that generate discomfort and impair clinical outcomes. Furthermore, extended chemical modifications may prevent the filler from being recognized as HA and could result in prolonged foreign body reactions.[31]

Finally, a correct injection technique is crucial to avoid the occurrence of both early and late adverse reactions. Bolus and pillar injections may cause granulomas and, generally, a rapid injection speed, an aggressive fanning technique, and a large bolus size increase the risk of late-onset reactions. Furthermore, inadequate aseptic procedures may increase the risk of nodules with bacterial aetiology; trauma can activate quiescent biofilms and exacerbate inflammation. Generally, the lips are a common site for late-onset nodules, whilst intramuscular injection may determine late-onset reactions.[31]

An expert panel discussed the stepwise approach to the management of late-onset reactions;[32] after the debate, the majority favoured dual antibiotic treatment consisting of a fluoroquinolone (e.g. ciprofloxacin 500 mg BID) with either a tetracycline (e.g. doxycycline or minocycline 100 mg/day) or a macrolide (e.g. clarithromycin 500 mg BID) for 3–6 weeks. Dissolution of a filler through intralesional hyaluronidase may be postponed by 24 h to 2 weeks after initiating the antibiotic treatment unless a more resistant HA (i.e. Vycross) has been injected, in which case intralesional hyaluronidase must be administered as early as possible. A dose of 30–300 units of intralesional hyaluronidase should be given per nodule. Second-line therapy may be based on intralesional steroids alone or combined with 5-fluorouracil and saline/lidocaine.[32]

Contraindications to the use of injectable HA fillers

Although injectable HA fillers are widely used and their safety profile is well-characterized, some patients present a higher risk of late-onset reactions. The use of injectable HA fillers is contraindicated in the presence of active autoimmune diseases, including rheumatoid arthritis, cutaneous vasculitis, systemic lupus erythematosus, psoriatic arthritis and systemic scleroderma. These patients may show a systemic inflammation status that may exacerbate the risk of late-onset reactions. However, a panel of experts noted that HA treatment could be considered if the disease is stable, not active and the patient has not experienced any flare-ups in at least 2 years.[31]

Localized scleroderma and Hashimoto disease, especially in the presence of high levels of antithyroid peroxidase and antithyroglobulin, represent moderate risk factors and HA fillers in these patients should be used with caution.[31] Diseases with low-grade fibrosis, such as

alopecia areata or vitiligo, are not considered contraindications for the use of HA fillers. Similarly, type 1 diabetes without any wound healing problem does not represent a concern for treatment.[31]

Rosacea, acne and dermatitis impair the barrier function of the skin and allow the penetration of infective agents. In these individuals, fillers should be injected with caution, especially in patients with hypertrophic scars or fibrotic tissue associated with excessive wound healing.[31]

Emerging trends and prospects of soft tissue fillers

Research in the field of skin and soft tissue ageing is continuously focused on finding novel applications of already available treatments and uncovering other novel targetable mechanisms of action.[33]

Amongst already available products, HA is versatile and suitable for developing new devices such as microneedles and microspheres. In drug delivery, biocompatible and effective HA-based microneedles promote skin hydration and overcome the hydrophobic interactions with the stratum corneum. Indeed, HA-based microneedles can be used to deliver macromolecules, such as vitamins, proteins, polysaccharides, DNA and drugs, and are largely employed in drug delivery and cosmetic fields.[34,35] HA microspheres exhibit great potential as microcarriers in terms of encapsulation efficiency and release kinetics as well as for cell distribution because of their excellent biocompatibility and degradability.[36] In the future, particle size, monodispersity, encapsulation rate, drug delivery ability, and industrial production of microspheres and microneedles must be optimized to broaden their applications in the bioengineering field.

Conclusions

Non-invasive techniques for the management of cutaneous ageing are growing in popularity across the world, and the availability of different therapeutic choices on the market necessitates a thorough understanding of each product's unique properties. HA-based fillers have a wide range of uses, a favourable safety profile and outstanding clinical outcomes. Each HA-based filler has rheological qualities that vary depending on the production process and are intended to produce precise effects in specific anatomical locations. The key problem for practitioners is the choice of fillers with the right characteristics to achieve the desired clinical outcomes. Given the widespread interest in cosmetics and skin ageing, the antiageing aesthetic business is developing many potential technologies and therapies, including advances in genetic therapy, cell-based therapy, platform technologies, biologics and personal care products. Future research can look at the safety and usefulness of these developments; for the time being, the best options for skin rejuvenation are non-invasive procedures with safe and effective products.

The Definisse™ filler range integrates advancements in cross-linking technology and rheological science, offering a scientifically grounded approach to facial rejuvenation. Through the application of XTR™ Technology and an understanding of material properties, the portfolio provides fillers tailored to specific aesthetic needs. By optimizing the degree of cross-linking to rheological characteristics, the formulations enable targeted versatility for various clinical applications.

Definisse™ fillers provide targeted solutions for aesthetic treatments: Definisse™ touch is suited for subtle, natural enhancements and soft lip volumization, ideal for first-time users; Definisse™ restore offers versatile, predictable rejuvenation for multiple targeted areas; Definisse™ core ensures precise structural contouring, delivering durable, stable results with high G-prime and ease of application. Together, they support a range of facial enhancement needs with tailored characteristics for patient comfort and satisfaction.

This approach underscores the importance of precision and safety in aesthetic treatments. The Definisse™ filler range exemplifies the application of scientific principles to enhance patient outcomes, supporting the continued evolution of evidence-based facial enhancement practices.

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References

1. Farage MA, Miller KW, Elsner P, Maibach H. Characteristics of the aging skin. *Adv Wound Care.* 2013;2:5–10. https://doi.org/10.1089/wound.2011.0356
2. Liang Y, Su W, Wang F. Skin ageing: a progressive, multi-factorial condition demanding an integrated, multilayer-targeted remedy. *Clin Cosmet Investig Dermatol.* 2023;16:1215–1229. https://doi.org/10.2147/CCID.S408765
3. Fenske NA, Lober CW. Structural and functional changes of normal aging skin. *J Am Acad Dermatol* 1986;15:571–585. https://doi.org/10.1016/s0190-9622(86)70208-9
4. Baumann L. Skin ageing and its treatment. *J Pathol.* 2007;211:241–251. https://doi.org/10.1002/path.2098
5. Okuda I, Akita K, Komemushi T, et al. Basic consideration for facial aging: analyses of the superficial musculoaponeurotic system based on anatomy. *Aesthet Surg J.* 2021;41:NP113–NP123. https://doi.org/10.1093/asj/sjaa305
6. Uitto J. Understanding premature skin aging. *N Engl J Med.* 1997;337:1463–1465. https://doi.org/10.1056/NEJM199711133372011
7. ISAPS. ISAPS International Survey On Aesthetic/Cosmetic Procedures Performed in 2023. https://www.isaps.org/media/rxnfqibn/isaps-global-survey_2023.pdf. Accessed December 2024.
8. Fundaro SP, Salti G, Malgapo DMH, Silvia I. The rheology and physicochemical characteristics of hyaluronic acid fillers: their clinical implications. *Int J Mol Sci.* 2022;23:20220910. https://doi.org/10.3390/ijms231810518
9. Salti G, Fundaro SP. Evaluation of the rheologic and physicochemical properties of a novel hyaluronic acid filler range with excellent three-dimensional reticulation (XTR) technology. *Polymers.* 2020;12:20200724. https://doi.org/10.3390/polym12081644
10. Kim JE, Sykes JM. Hyaluronic acid fillers: history and overview. *Facial Plast Surg.* 2011;27:523–528. https://doi.org/10.1055/s-0031-1298785
11. Duffy DM. Silicone: a critical review. *Adv Dermatol.* 1990;5:93–107; discussion 108-109.

12. Webster RC, Gaunt JM, Hamdan US, Fuleihan NS, Smith RC. Injectable silicone for facial soft-tissue augmentation. *Arch Otolaryngol Head Neck Surg.* 1986;112:290–296. https://doi.org/10.1001/archotol.1986.03780030054011
13. Peters W, Fornasier V. Complications from injectable materials used for breast augmentation. *Can J Plast Surg.* 2009;17:89–96. https://doi.org/10.1177/229255030901700305
14. Cahill KV, Burns JA. Volume augmentation of the anophthalmic orbit with cross-linked collagen (Zyplast). *Arch Ophthalmol.* 1989;107:1684–1686. https://doi.org/10.1001/archopht.1989.01070020762044
15. Kontis TC. Contemporary review of injectable facial fillers. *JAMA Facial Plast Surg.* 2013;15:58–64. https://doi.org/10.1001/jamafacial.2013.337
16. Marinelli E, Montanari Vergallo G, Reale G, et al. The role of fillers in aesthetic medicine: medico-legal aspects. *Eur Rev Med Pharmacol Sci.* 2016;20:4628–4634.
17. Lourith N, Kanlayavattanakul M. Biopolymeric agents for skin wrinkle treatment. *J Cosmet Laser Ther.* 2016;18:301–310. https://doi.org/10.3109/14764172.2016.1157369
18. Tagle JM, Macchetto PC, Duran Paramo RM. Clinical performance of a dermal filler containing natural glycolic acid and a polylactic acid polymer: results of a clinical trial in human immunodeficiency virus subjects with facial lipoatrophy. *J Clin Aesthet Dermatol.* 2010;3:42–47.
19. Briden E, Jacobsen E, Johnson C. Combining superficial glycolic acid (alpha-hydroxy acid) peels with microdermabrasion to maximize treatment results and patient satisfaction. *Cutis.* 2007;79:13–16.
20. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: a key molecule in skin aging. *Dermatoendocrinology.* 2012;4:253–258. https://doi.org/10.4161/derm.21923
21. Hong GW, Wan J, Park Y, et al. Manufacturing process of hyaluronic acid dermal fillers. *Polymers.* 2024;16:20240927. https://doi.org/10.3390/polym16192739
22. Definisse™ touch filler +lidocaine. https://www.relife-aesthetics.com/corporate/en/products/definisse-fillers.html. Accessed July 22, 2025.
23. Definisse™ restore filler +lidocaine. https://www.relife-aesthetics.com/corporate/en/products/definisse-fillers.html. Accessed July 22, 2025.
24. Definisse™ core filler +lidocaine. https://www.relife-aesthetics.com/corporate/en/products/definisse-fillers.html. Accessed July 22, 2025.
25. ClinicalTrial.gov. Wrinkle | Hyaluronic acid filler. https://clinicaltrials.gov/search?cond=Wrinkle&intr=Hyaluronic%20acid%20filler. Accessed December 2024.
26. Salti G, Siquier-Dameto G, Rharbaoui S, et al. An interim 6-month analysis of the dermatologic effects and midface volume correction with XTR CL filler in a prospective, single-center study. *Dermatol Surg.* 2023;49:943–948. https://doi.org/10.1097/DSS.0000000000003878
27. Siquier-Dameto G, Salti G, Rharbaoui S, et al. A 12-month analysis of the dermatologic effects and durability of midface volume correction with DEF CL volumizing filler in a prospective, single-center study. *Dermatol Surg.* 2024;50:1131–1136. https://doi.org/10.1097/DSS.0000000000004307
28. Muti GF. Midface 3D restoration with an innovative high G' filler. *J Cosmet Dermatol.* 2021;20(Suppl. 2):7–11. https://doi.org/10.1111/jocd.14282
29. Bhojani-Lynch T. Late-onset inflammatory response to hyaluronic acid dermal fillers. *Plast Reconstr Surg Glob Open.* 2017;5:e1532. https://doi.org/10.1097/GOX.0000000000001532
30. Convery C, Davies E, Murray G, Walker, L. Delayed-onset nodules (DONs) and considering their treatment following use of hyaluronic acid (HA) fillers. *J Clin Aesthet Dermatol.* 2021;14:E59–E67.
31. Baranska-Rybak W, Lajo-Plaza JV, Walker L, et al. Late-onset reactions after hyaluronic acid dermal fillers: a consensus recommendation on etiology, prevention and management. *Dermatol Ther.* 2024;14:1767–1785. https://doi.org/10.1007/s13555-024-01202-3
32. Artzi O, Cohen JL, Dover JS, et al. Delayed inflammatory reactions to hyaluronic acid fillers: a literature review and proposed treatment algorithm. *Clin Cosmet Investig Dermatol.* 2020;13:371–378. https://doi.org/10.2147/CCID.S247171
33. Khetpal S, Ghosh D, Roostaeian J. Innovations in skin and soft tissue aging-a systematic literature review and market analysis of therapeutics and associated outcomes. *Aesthetic Plast Surg.* 2023;47:1609–1622. https://doi.org/10.1007/s00266-023-03322-1
34. Fonseca DFS, Vilela C, Pinto RJB, et al. Bacterial nanocellulose-hyaluronic acid microneedle patches for skin applications: in vitro and in vivo evaluation. *Mater Sci Eng C Mater Biol Appl.* 2021;118:111350. https://doi.org/10.1016/j.msec.2020.111350
35. Saha I, Rai VK. Hyaluronic acid based microneedle array: recent applications in drug delivery and cosmetology. *Carbohydr Polym.* 2021;267:118168. 20210507. https://doi.org/10.1016/j.carbpol.2021.118168
36. Hamilton M, Harrington S, Dhar P, Bittel LS. Hyaluronic acid hydrogel microspheres for slow release stem cell delivery. *ACS Biomater Sci Eng.* 2021;7:3754–3763. https://doi.org/10.1021/acsbiomaterials.1c00658