# Longevity of hyaluronic acid dermal fillers – current state of knowledge

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## ABSTRACT

**Introduction:** Hyaluronic acid, is the most abundant glycosaminoglycan in the human body that is highly hydrophilic, with 50% amount located in the dermis. Skin aging is naturally accompanied by hyaluronic acid reduction, which could accelerate the dehydration, loss of elasticity, and wrinkling of the skin. The injection of dermal fillers gives desirable cosmetic outcomes by erasing skin rhytides or restoring facial volume loss, or both. Hyaluronic acid-based filler was launched because of its characteristics. The aim of the study was to find available data regarding longevity and changes over time of hyaluronic acid deposits in skin of patients that underwent hyaluronic acid injection.

**Methods:** A systematic review of the published literature was conducted in accordance with the PRISMA guidelines. The literature search was performed in June 2023 and included PubMed and Google Scholar databases.

**Results:** Our analysis included 8 studies involving different hyaluronic acid formulations and different assessment methods of longevity and diffusion patterns of hyaluronic acid. Hyaluronic acid fillers turned out to be longer lasting than 12 months with cases exceeding more than 2 years lifespan. Different methods of evaluation can be used to assess post- injection results. These include MRI, high- frequency ultrasound, 3D imaging as well as Wrinkle Severity Rating Scale changes and subject- reported satisfaction. Delayed complications of hyaluronic acid, injections are rare. It is important for practitioners to note the possibility of them occurring even after more than 2 years post-injection.

**Conclusions:** There is indication that hyaluronic acid fillers may be longer lasting than previously thought and this should be considered when preparing treatment plans for patients and diagnosing potential long-term adverse effects.

**Key words:** hyaluronic acid, longevity, dermal filler, skin aging, HA filler.

## INTRODUCTION

Hyaluronic acid (HA), is the most abundant glycosaminoglycan in the human body that is highly hydrophilic, with 50% amount located in the dermis [1, 2]. Hyaluronic acid is involved in several important biological functions, such as the regulation of cell adhesion and motility, the manipulation of cell differentiation, and cell proliferation [3]. Skin aging is naturally accompanied by hyaluronic acid reduction, which could accelerate the dehydration, loss of elasticity, and wrinkling of the skin. Key factors of this process include the resorption of structural support, the redistribution of facial fat, the action of gravity, hormonal changes, and the influence of environmental factors such as smoking and sun exposure [4].

The application of dermal fillers is becoming an increasingly popular technique for facial rejuvenation. This procedure is relatively noninvasive and provides excellent three-dimensional restoration of facial volume, rebalances facial proportions and symmetry, and reduces fine lines and wrinkles. The injection of dermal fillers gives desirable cosmetic outcomes by erasing skin rhytides or restoring facial volume loss, or both. The commonly injected sites on the face include the perioral area, periocular region, nasolabial folds, malar fat pad, marionette lines, glabella, and lips [5]. The rising demand for aesthetic procedures has led to the introduction of multiple injectable dermal fillers on the market.

Hyaluronic acid -based filler was launched because of its characteristics, including its biocompatibility, non-teratogenicity, sterility, chemical inertness, safety, durability, stability, reversibility, ease of application, and good cost/benefit ratio; in addition, this filler was non-migratory or non-modifying based on tension or organic substances and was approved by sanitary authorities. It is highly biocompatible without tissue specificity [6].

Many HA fillers are commercially available, each differing in HA concentration, the degree of cross-linking, and particle size which ultimately contribute to essential gel properties such as hardness, cohesiveness, and swelling ratio. Products with high gel hardness and cohesivity provide structure and support. It is important for physicians to understand the change in facial profile from these filler products over time, to maximize their clinical performance, cosmetic outcome and to properly assess the timeframe of potential long- term side effects of HA filler injection [7]. However, there are limited details and clinical evidence regarding postinjection dermal changes in addition to the longevity and diffusion pattern of hyaluronic acid filler over time [8].

Aim of this review is to find available data regarding longevity and changes over time of HA deposits in skin of patients that underwent HA injection.

## METHODS

A systematic review of the published literature was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The literature search was performed in June 2023 and included PubMed and Google Scholar databases. The Medical Subject Headings (MeSH) terms used were "cheek" OR "midface" OR "malar" OR "lip" OR "nasal" OR "NLF" OR "longevity" OR "long- term" OR "filler" OR "hyaluronic acid". Various combinations of key terms were used to narrow down search results. Studies were included if they met the following criteria: (1) reported patient data on the use of HA fillers, (2) included human patients (3) published in the years 2000 to 2023. Exclusion criteria included studies that (1) were published in languages other than English, and (2) involved supplemental augmentation techniques such as botulinum toxin injections or resurfacing. All titles and abstracts were screened for relevance, and duplicates between databases were removed. Full-text articles for the remaining studies were reviewed. The reference lists of the full-text articles were analyzed for any additional relevant studies. All studies that met the specified criteria were included in the analysis.

## RESULTS

Our analysis included 8 studies involving different HA formulations and different assessment methods of longevity and diffusion patterns of HA.

Da Costa *et al.* compared three different types of hyaluronic acid fillers (biphasic, monophasic monodensified and monophasic polydensified) in skin in order to assess intradermal durability and compare the products over 6 months [6]. In all, 25 volunteers received equal injections of three different fillers in the dermis of the right lumbar region into three different sites, yielding nine points of application in each patient. Each line was biopsied on days 2, 92 and 184 and then samples were analyzed histologically. The amounts of biphasic, monophasic monodensified, and monophasic polydensified fillers decreased by 12.5%, 25%, and 62.5%, respectively, over a period of 182 days after injection. Interestingly, the amount of monophasic polydensified filler was equal to that of the monophasic monodensified filler at three months after injection, but the amount of monophasic monodensified filler remaining after six months exceeded that of the monophasic polyden-

sified filler. This study showed significant differences in *in vivo* longevity of different types of hyaluronic acid fillers that are most commonly used worldwide.

Rho *et al.* used facial images to evaluate and compare efficacy and longevity of two different HA fillers in improving the nasal profile in Asians [7]. Twenty-eight Korean women underwent rhinoplasty with either monophasic monodensified or biphasic HA filler with no touch ups during the 48 week observation period. Assessments including patient satisfaction and three-dimensional (3D) imaging analysis were performed before, immediately after, 2 weeks, 12 weeks, 24 weeks, and 48 weeks after filler rhinoplasty. Both products proved to be compatible effectively, but conversely to expectations, monophasic monodensified HA was superior to biphasic HA in radix elevation long term. Although the effect of injections of both HA filler types lasted over 48 weeks (as assessed by 3D imaging), authors recommended a touch-up at 3 months follow-up since subject satisfaction declined sharply after 24 weeks. This shows possible dissociation between patients' satisfaction and visible effects of HA injection leading to subjects' urge to repeat treatment risking overfilling of the same area and accumulation of HA deposits.

Different method to analyze volume changes after HA injection was used by Qiao *et al*. [8]. The authors evaluated the longevity and diffusion pattern of two hyaluronic acid fillers generated by different cross-linking technologies used in the treatment of nasolabial folds using high-frequency ultrasound. Forty-one subjects were treated with Restylane 2 and the remaining 41 were treated with Dermalax DEEP. Compared with Restylane 2, Dermalax DEEP has a greater cross-linking percentage and a larger particle size because of different bonding technology. Wrinkle severity rating scale score and high-frequency ultrasound evaluation of nasolabial folds were performed before and after the injection of hyaluronic acid filler. The ultrasound images were acquired and analyzed to determine dermal thickness and the shape and distribution of hyaluronic acid filler. At 2 and 24 weeks from baseline, increased dermal thickness induced by hyaluronic acid filler treatment were 0.57 ±0.20 and 0.27 ±0.18 mm in the Restylane 2 group and 0.59 ±0.15 and 0.34 ±0.14 mm in the Dermalax DEEP group, respectively and was not significantly different between groups. At 48 weeks after injection, increased dermal thicknesses of the Restylane 2 group (0.14 ±0.12 mm) were much lower than those of the Dermalax DEEP group (0.20 ±0.13 mm). Restylane 2 tended to form a more diffuse pattern, with multiple smaller bubbles, whereas Dermalax DEEP developed into a more localized configuration, with larger clumps.

Due to its excellent soft tissue discrimination and the possibility to obtain quantitative data, magnetic resonance imaging (MRI) is increasingly used for the evaluation of injectable dermal fillers [9]. MRI with T2 W and contrast-enhanced T1 W sequences can accurately assess the volumetric and temporal changes of subdermal HA filler injection. Because of its high water content, HA filler appears strongly hyperintense on T2 W and STIR sequences and hypointense on T1 W sequences. Injected HA typically shows well-defined serpiginous margins at imaging.

Becker *et al.* evaluated MRI findings of HA injection used for the correction of HIV- associated facial lipoatrophy in 10 patients [10]. Subjects underwent subdermal injection into a submalar area of 1.3 ±0.6 ml filler per side and had MRI examinations prior to and then 1, 6 and 12 months after injection. The volume was maximal in the first month and remained more or less stable for the next 12 months. Using 3D fat-saturated T2 W sequences, HA was found in anatomical regions situated much deeper than the compartment of the initial injection. The hydrophilic nature of HA and the diffusion permeability of the fibrous septae between the facial fat compartments are thought to be responsible for this finding. As HA binds water *in vivo* and as the filler also induces *in vivo* procollagen formation (which has high water content), MRI actually depicts a mixture of all three substances (injected HA, bound water, and *de novo* formed procollagen) and differentiation between these three components is not possible with MRI 5.

In different study Abramo *et al.* used MRI to analyze gel diffusion and degradation of HA injected into NLF of 10 female patients [11]. HA was applied into the superficial compartment of the subcutaneous fat of NLF. Each patient received three injections on both sides. A bolus injection technique without retrograde backflow applied per injection point 0.15–0.20 ml of HA for moderate NLF and 0.20–0.25 ml for severe NLF. Largest longitudinal and transverse axes of deposits were measured in MRI. The longitudinal and transverse axes at month twelve were 61.11% and 58.41% smaller than 1 month after application indicated the slow degradation of the HA within twelve months. Despite reduction in size the small amount of gel was still present in subcutaneous fat after 12 months indicating efficacy and longevity of HA NLF rejuvenation.

Master *et al.* presented a case report of HA injected in the subcutaneous fat of the lateral face, deep fat compartments of the mid-face, and a combination of deep and superficial injection of HA in the chin [12]. Using MRI they demonstrated longevity of HA in the lateral face and deep fat compartments of the mid-face versus almost complete degradation of HA in the chin 19 months after injection. The MRI signal demonstrated no migration of HA and persistence of HA at 27 months in the lateral face and mid-face.

Delayed complications include inflammation or infection that can occur months to years after HA filler injection. Delayed infections are thought to be the result of biofilms forming on the filler deposit, potentially associated with multiple needle passes or poor aseptic technique [13]. These biofilms may remain dormant for weeks to years before being "activated" by trauma, hematogenous spread of an existing infection, or a compromised immune system, resulting in local infections like cellulitis or abscesses.

Park *et al.* treated 28 cases of HA- filler- related complications [14]. Among the patients 3 of them had complications 1 year, 1 of them 15 months and 1 of them as late as 2 years after HA injection. These complications were palpable masses with one case of tissue necrosis.

Kalmanson *et al.* described a case of filler- exacerbated facial cellulitis that occurred 2.5 years after HA filler injection over the zygomas [15]. Residual HA filler was confirmed by MR imagining and the appearance of it was consistent with that described in the literature as T2 hyperintense. These cases indicate that HA filler may be longer lasting than described and delayed complications after HA injection shouldn't be immediately ruled out even years after

## DISCUSSION

In our study, the systematic search according to the PRISMA guidelines yielded 8 eligible articles, two of which were case reports. Hyaluronic acid fillers turned out to be longer lasting than 12 months with cases exceeding more than 2 years lifespan. Longevity of HA depends on various factors including injected volume and site of injection. More mobile facial regions correspond to faster degradation of HA. Furthermore, there are significant differences in diffusion and durability of different types of HA. Higher concentration and cross-linking of HA result in more resistance to enzymatic degradation [16]. In some facial regions such as submalar area HA can be found much deeper than initial depth of injection would suggest. This indicates that HA diffuses not only horizontally, in one layer, but also between compartments. Different methods of evaluation can be used to assess post-injection results. These include MRI, high- frequency ultrasound, 3D imaging as well as Wrinkle Severity Rating Scale changes and subject- reported satisfaction. While MRI isn't cost effective method to examine HA deposits it is best in eliminating human error. Delayed complications of HA injections are rare. It is important for practitioners to note the possibility of them occurring even after more than 2 years post-injection. It is advised to consider the presence of HA filler in all patients, as the use of hyaluronidase earlier in the course of treatment can save the patients suffering from HA complications considerable morbidity and multiple days of hospitalization.

This systematic review has a few limitations. First, there was significant heterogeneity is the injection depth (i.e., submuscular, subcutaneous), injection technique (i.e., blunt cannula, needle), site of administration (i.e., submalar, NLF, nasal, lateral, medial), administration technique (i.e., bolus, fanning, serial puncture), and physician's expertise across studies. Therefore, the reported outcomes and AEs may not be reliably compared. Second, the quality of the included studies was limited by the small sample size and homogeneity of patients. Third, one study evaluated their results on subjective measurements such as patient satisfaction. While patients' perceived degree of improvement is clinically relevant, the subjective nature of these results creates inherent challenges when comparing results across studies. Future studies should include objective outcome measures and more diverse patient samples.

## CONCLUSIONS

This systematic review evaluated longevity and onset of delayed complications in different HA fillers used for facial rejuvenation. There is indication that HA fillers may be longer lasting than previously thought and this should be considered when preparing treatment plans for patients and diagnosing potential long- term adverse effects. Due to variability in technique and product types no maximal durability of injected HA could be concluded. Additional studies are required to conclusively determine degradation patterns of different HA in different facial rejuvenation procedures.

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## ETHICAL APPROVAL

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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