Sawa Medical Journal

Reprint from

Vol.2 Issue.1 2026

ISSN : 3007-4738 (online)

Article Review: Histopathological Change in Tissue After Injectable Hyaluronic Acid (Dermal Filler)

Asawer Abdul-Jabbar Al-Salman

Department of Pathological Analysis, College of Science, Wasit University, Iraq

Article Information
Received: 15-2-2026
Accepted: 1-3-2026
Published: 1-4-2026

Abstract

Injectable fillers in the current times are now a pillar in facial rejuvenation and play a key role in ensuring the success of the treatment. Although their advantages are undeniable, the list of potential complications (adverse effects that are instant, late, delayed, transient or irreversible) is too long and must be taken into consideration. The distinction is made between the different filler material, these effects are attributed to findings of the histopathology and to the existing treatment options.

Background

Injectable hyaluronic acid is one of the temporary dermal fillers. The concentration of hyaluronic acid can be found naturally in all parts of the body with the highest concentration found in the joints, eyes and the skin. Hyaluronic acid injected is intended to minimize the effect of fine lines, wrinkles, folds of the face, structure, framework, and volume of the face and lips.

Aims: In order to assess the degradation and alterations within the tissue after hyaluronic acid (HA) filler injections with special attention paid to crosslinking agents, degradation and tissue reactions..

Keywords: HA, Tissue, Dermal filler, Histopathological change.

1. Hydroxyadenosine Dermal Filler

Glycosaminoglycan HA has a high molecular weight and is straight and unbranched. The components are N-acetyl-D-glucosamine and D-glucuronic acid. Anything living should be able to withstand it, in theory, because it is a biological molecule that is not species specific. The normal glycosaminoglycan moiety is connected with species-specific proteins, and the method of its synthesis is also highly important. Depending on the molecular size, HA, a naturally occurring biological filler, can have far-reaching effects on living organisms. Inflammation occurs when the particles are little, but it does not occur when they are

long (Clark, 2007). There is need to stabilize the use of HA fillers, and the mode and extent of stabilization casts doubt on the tolerability of HA. (Stern *et al*., 2006). Hyaluronic acid skin filler This is a hyaluronic acid dermal filler that is injected into the skin to retard aging. HA based dermal fillers are able to elevate the skin surface and shape in addition to sealing gaps of the tissue. The retention of water, a finding of the hydrophilicity of HA induces the moisturizing effect of the skin and the volume of the dermal filler (Mero *et al.,* 2014).

Hyaluronic acid-derived dermal fillers are readily injectable, do not cause immune reactions, as well as are biocompatible with the body. They are side effects and very soluble in water which makes them the perfect choice in plumping of skin as well as other soft tissues (Song *et al.,* 2013). Hyaluronic acid (HA) is a good dermal filler, and it can be used in a wide variety of other medical applications, including biology of sarcomas, wound healing, tissue engineering, and drug delivery systems, due to its compatibility with the human body (Valachova *et al.,* 2020). The breakdown of the native HA polymer occurs rapidly by using enzymes to degrade the macromolecule and has a half-life of twenty four hours on the skin (Zamboni *et al.,* 2017). HA is a cross-linked As biomaterials or implanted device as hydrogel so as to demonstrate better biological functioning and enhanced biodegradation resistance (Papakonstantinou *et al.,* 2012). These hydrogels have been developed with the aid of various cross-linking methods that incorporate the use of such chemical agents as poly (ethylene glycol) diglycidyl ether, divinyl sulfone, 1, 4-butanediol diglycidyl ether (BDDE) and, more recently, bis (2 isocyanatoethyl) disulphide (Khunmanee *et al*., 2017). The cosmetic medicine is more concerned with longevity and stability of HA dermal fillers when they have been implanted into the tissues. The safety profile known and good stability of BDDE has led to its approval in many regulatory bodies, and thus it is the primary cross-linker used in the stabilisation of most HA dermal fillers on the market. Clinical studies have demonstrated that it is safe to use at least one year on dermal fillers based on hyaluronic acid cross-linked with 10 BDDEs (Zamboni *et al.*, 2020). Cosmetic and medicinal uses of hyaluronic acid (HA) gel fillers have been expanding since the early 2000s to include correction of folds and wrinkles as well as volume loss in the cheeks, lips, and other areas affected by aging (Zamboni *et al*., 2021). New HA fillers vary greatly in hardness and physicochemical characteristics; in most cases, different filler products from the same series have different therapeutic indications for different tissues (De Boulle *et al.,* 2013). For instance, HA dermal fillers are ideal for correcting facial volume since they are formulated for injection into deep layers of skin, like the supraperiosteal and subcutaneous zones (Segura *et al*., 2012). On the flip side, tiny superficial wrinkles and an imbalance in skin moisture are best addressed with HA dermal fillers designed for superficial injection. There have been a lot of clinical and pre-clinical studies looking at the effectiveness of different HA dermal fillers on the market, but most of them have focused on how long the fillers last and how much they can swell (Merola *et al.,* 2018; Mochizuki *et al.,*2018; Ryu *et al.,* 2021).

Without considering other factors connected to the filler's performance or clinical behavior, durability only quantifies the in vivo residence duration by assessing the residual volume at the injection site. Because of this, relying only on durability assessments to determine the overall effectiveness of hyaluronic acid dermal fillers is not suitable (Dugaret *et al.,* 2018). Testing how well HA dermal fillers blend with surrounding tissue is becoming more popular. When discussing the "distribution pattern within biological tissue, particularly the manner in which the filler material interweaves with dermal fibers," the terms "tissue integration" and "bio-integration describe the same thing. Problems with textural changes, such as superficial beading and lump development, have been associated with HA dermal fillers in therapeutic

applications (Flynn *et al.,* 2011). Hence, a thorough examination of tissue integration is essential, especially for determining the general safety and success of new dermal fillers. The pattern of dispersion and assimilation of HA dermal fillers inside the tissue has only been established in a small number of trials that have used four or fewer products so far (Micheels *et al.,* 2012). Majority of many clinical and pre-clinical trials that have been undertaken to investigate the efficacy of various commercialized dermal fillers have principally been focused on the swelling capacity and longevity of the fillers (Merola *et al.,* 2018; Mochizuki *et al.,*2018; Ryu *et al.,* 2021).
Durability is a measure of the in vivo residence time simply by determining the residual volume at the site of injection without taking into account other aspects relating to the performance of the filler or the clinical behavior. Due to this, it is not appropriate to use durability tests to calculate the total efficacy of HA dermal fillers. There is an increasing popularity of testing the ability of HA dermal fillers to mix with the surrounding tissues. Tissue integration and bio-integration which are used to denote the same term are used when speaking about the distribution pattern of biological tissue, i.e. the way of how the filler material penetrates dermal fibers. Issues of textural alterations, including the formation of superficial beads, and lumps have been observed with HA dermal filler in treatment. Therefore, it is critical that there be an in-depth study of the tissue integration particularly in the context of identifying the overall safety and efficacy of new HA dermal fillers. The dispersion and assimilation pattern of the dermal fillers in the tissue has been established only in few trials that have utilized four or less products so far (Micheels *et al.,* 2012).

2. Changes in Histology of Human Tissue Reaction to Hyaluronic Acid Fillers

All forms of mammals have hyaluronic acid. Although they are not species-specific, HA are associated with species-specific proteins. Effective preparations may not include any extraneous proteins. They are not quite likely to lead to granulomas, despite having several temporary side effects, including infections and random granulomas (Rodrigues-Barata and Camacho-Martínez, 2013). Currently, it has over 200 products in the market. To evade the ill side effects, you must select popular brands that are reputed to be of good quality. The reason is that the possibility of problems is considerably reduced. Individuals are not supposed to use products of low quality which are not tested. The most popular fillers in the moment are hyaluronic acid preparations. Typically, they are employed on a six-month basis, although this may vary greatly depending on the magnitude of the molecules, as well as the way they are connected to each other. Some of the variations include molecular size, protein concentration, chemical bonding, and fluidity, whether or not the substance is monophasic or biphasic, the pain associated with injection, and the beading as well as lumping. Due to this reason, special attention should be paid to the observation of the tissues integration especially when it comes to the assessment of the global safety and efficacy of the newly developed HA dermal filler. To date, only a handful of studies that involved the use of 4 or more products studied the character of HA dermal filler spreading, and its incorporation in the tissue (Signorini *et al*., 2016). The occurrence of granulomas can be eliminated by making sure that a good preparation is achieved. does not combine (Fig.1). When first launched, granulomas were widespread with non-animal-derived synthetic HAs. However, since a new product came out about three years ago, they have become extremely rare. This leads to granulomas that look like foreign bodies and have a lot of eosinophils and large cells that contain hyaluronic acid (Fig. 2).

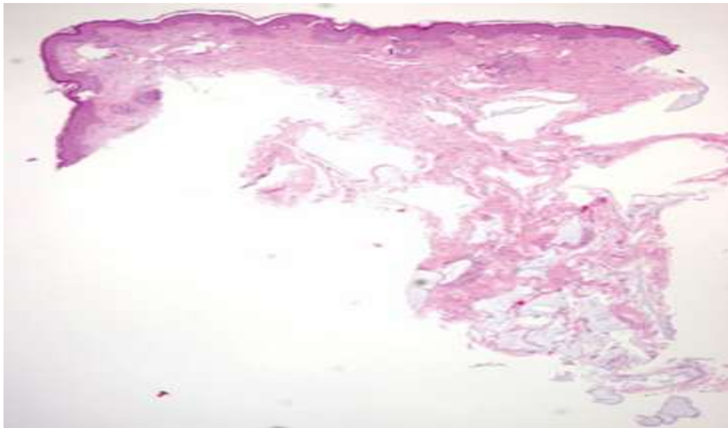

Figure1: A slightly bluish to skin-colored lump in the dermis that has been biopsied on the suspicion of basal cell carcinoma (HE stain): hyaluronic acid.

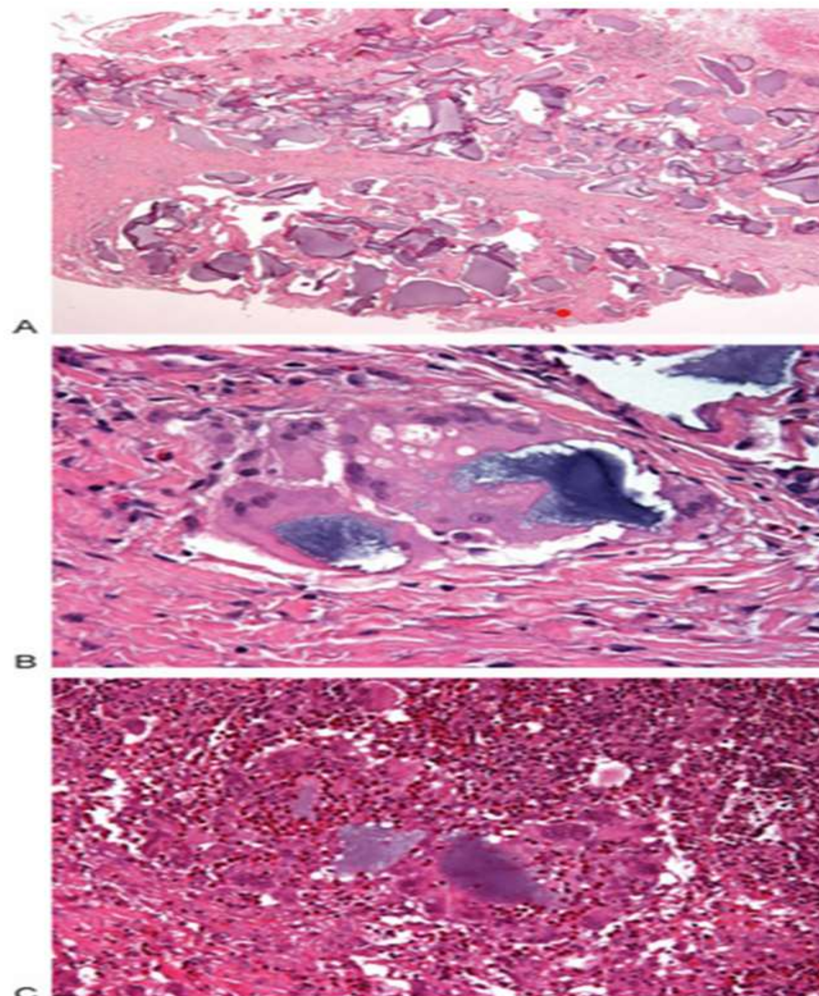

Figure 2: (A) A reaction characterized by inflammation and granulomatous inflammation to hyaluronic acid HE (B) Engulfment of clumped hyaluronic acid by the foreign body giant cells (C) Swallowed hyaluronic acid and a strong eosinophilic infiltration, epithelioid cells and foreign body giant cells are visible.

The body of human beings has a cascade of responses to fillers injection, which contains edema, inflammation, biostimulatory, foreign body reactions, and capsule formation. When a tissue response to

an unknown foreign body invader first sets in, the plasma proteins adsorb to the surface of the object. This leads to the activation of monocytes and macrophages, which are two forms of phagocytes and surrounds the invader. This results into the fusion of the phagocytes, to form large cells having multiple nuclei. The production of collagen, which is also referred to as foreign body reaction, involves the formation of a strong capsule that entirely surrounds the foreign body (Buntrock *et al.,* 2013).

Because HA is a naturally occurring polymer, it is not as likely to cause an adverse reaction in the body as synthetic polymers such as PLLA or PCL, which are recognized to result in more serious side effects and a faster rate of collagen formation when used as long-term fillers. It is common to see the formation of a capsule surrounding the injectable filler four weeks after injection, as revealed under a microscope analysis of tissue reactivity to the filler. A structure hypothesized to be generated by compressed tissue beneath the skin appears as a surface layer shortly after therapy. A lattice structure is formed after four weeks by fibroblasts, neovascularization, and collagen renewal. The HA filler is gradually replaced by normal tissue, which consists of fibroblasts, connective tissue, adipocytes, and blood vessels, as it dissolves and is absorbed (Lee and Kim, 2015). In the first eight weeks after HA filler injection, there is a dramatic increase in changes to Type III collagen, which are seen in the initial phases of wound healing. Approximately 13.8% of the filler volume is collagen after four weeks, and that number grows to about 21.5% after thirty two weeks, when it accounts for the majority of the filler volume (Artzi *et al*., 2016). These results support the concept that tissue response of the body serves as a substitute of HA fillers inserted into the body to an extent. Now it can be said that HA fillers may last more than a year or two, but it may depend on the part of the face and the type of tissue. Remember that, whatever space has been filled in with autologous tissue can never be the same as it used to be prior to the injection regardless of the duration of time (Seo, 2021). The reality that the effects of the HA filler do not disappear as fast as is expected in some patients, suggests that there is a healthy reaction to their tissue. The outcome of this reaction is the replacement of the filler mass with the tissue of the patient and the formation of a firm capsule around the filler mass through the process of collagen regeneration. Apparently, this would stop the hyaluronidase enzyme, which is only active in the surface of the mass, to break down and absorb the HA filler (Ablon, 2016).

Ideally, I would prefer to create a thicker capsule to enclose the filler mass and replace it. Nevertheless, in reality, such a practice is not necessarily a good idea as it may result in biofilm infections. The most successful and safest method of inducing moderate levels of capsule formation is by returning the tissue to its pre-injection state (Baijens *et al.,* 2007). Reactions in healthy tissues after filler injection maintain the amount of the filler and prolong its duration. The conventional wisdom held that HA fillers would eventually go away after a few of months. However, it is now known that cells in the body undergo changes over time, which means that the filler's autologous tissue also undergoes modifications. To maintain the desired appearance, the fillers can be changed as required (Petrey *et al.,* 2014). Patients are now satisfied with the long-term results of filler injections as they don't require frequent touch-ups and their appearance doesn't undergo a radical transformation with time. Practitioners should consider the following factors when selecting and administering HA filler products: the injection site, the state of the patient's skin and soft tissues, the injection layer, the physical characteristics of the filler, and the injection method, any external factors that could impact the injection site, and the patient's body's reaction to the tissue. Both the volume change and the longevity of the filler can be affected by these circumstances; ideally, it would be best if the filler could be returned to its pre-injection state (Baijens *et al.,* 2007).

3. Fillers' Unsafe Effects and Their Histopathology

The worst outcomes of DMost do not correlate directly with a particular filler but, instead, with volumetric increase or other technical complications, such as improper placement, improper injection, improper identification of indications, and infections caused by ice and water contamination (Grippaudo *et al.,* 2013). Radio-labeled leukocyte scintigraphy is the most appropriate technique in order to distinguish between infections and other nodules and granulomas (Colbert *et al.,* 2013). The adverse effects may be immune-mediated and inflammatory and may take some time to manifest themselves. Most frequent observations are oedema, granulomas, sarcoid-like reactions and panniculitis (Fig. 3, Fig. 4). Discussing unusual filler-related complications such as systemic granulomatous and autoimmune diseases, as well as rare acute hypersensitivity reactions, the professionals are recommended to consider the injection site, the condition of the skin and other soft tissues, the depth of the injection, the physical properties of the filler, the injection procedure, external flow at the injection site, and the body reaction to the filler. These variables are capable of influencing the variation in the filler length and volume, preferably to the original position before the filler injection (Grippaudo *et al.,* 2013). Various fillers possess varying patterns and/or morphologies of skin stains. This not only affects the delayed reactions such as granulomas, abscess infections, but also the sudden reactions when the filler is viewed. Bovine collagen is considered to be a thick eosinophilic mesh in the dermis. It is not birefringent as are human collagen fibers. The first type of allergies is normally lymphocyte infiltration, which may result in the development of granuloma, which is marked by a number of multinucleated giant cells and numerous epithelioid cells. In some instances hyaluronic acid may be found in the skin, a very amorphous basophilic material, perhaps exhibiting the Tyndall effect where it is applied to the surface. Probably due to the protein concentration, granulomas could frequently be identified at the initial stages of streptococcal HA production (Requena *et al.,* 2011).

Figure 3: HEMA granulomas two years post-injection.

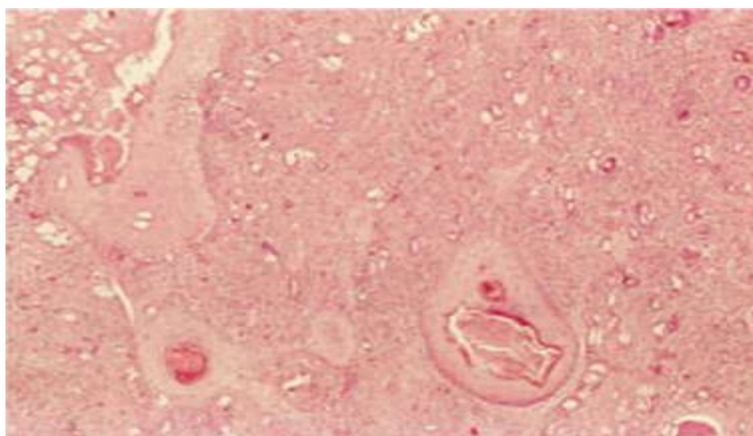

Figure 4: HEMA granulomas: a dense granulomatous infiltration characterized by epithelioid cells and HEMA particles, stained with H&E at 100x magnification.

4. Imaging Methods

In order to help diagnose filler concerns, including the possible presence of abscesses, multiple imaging modalities were used. Scarring, overfilling, migration, and foreign-body granulomas are further signs (Ginat and Schatz, 2012). A combination of high-frequency ultrasound, magnetic resonance imaging (MRI), and white blood cell scintigraphy was utilised to distinguish between infections, fibrosis, granulomatous inflammation, and product migration (Grippaudo *et al.,* 2014). It contains radio-opaque calcium hydroxyapatite, which can be observed in routine radiographs (El-Halaby and Furtado, 2014). But injecting it can create localised hypermetabolism, which can fool positron emission tomography scans (Damrose, 2008). By traditional X-ray film, CT scans, and MRI, it is usually possible to distinguish between various materials (Ginat and Schatz, 2013).

Conclusions

Among the most popular items in visual medicine is fillers. Clients are healthy individuals who wish to look better following surgery, not sick people. For both the patient and possibly the treating physician, any negative outcome—whether immediate, delayed, temporary, or permanent—is tragic. To get rid of them, every effort must be made. The physician needs to be well-versed in using the best product, according to the guidelines, avoiding any contraindications, using the proper aseptic injection techniques, and ensuring that each filler is positioned correctly. When receiving treatment, the patient must adhere to the doctor's directions. Giving the patient a filler pass that details the type of filler, when, and where it will be injected would be the most effective way to do this. Regardless of your level of caution, awful things can still happen. Consider them and pay attention to what a patient has to say. The therapy must start as soon as possible. Further studies using a larger sample size of individuals from various ethnic origins are required to validate the findings and examine the long-term effects of HA fillers on tissues.

References

A. C. Petrey and C. A. de la Motte. Hyaluronan, a crucial regulator of inflammation. Frontiers in Immunology 2014; (4):101.

Artzi, C. Loizides, I. Verner, and M. Landau. Resistant and re current late reaction to hyaluronic acid-based gel. Dermatologic Surgery. 2016; 42 (1):31–37.

Baijens L, Speyer R, Linssen M, Ceulen R, Manni JJ. Rejection of injectable silicone “Bioplastique” used for vocal fold augmenta tion. Eur Arch Otorhinolaryngol 2007;264(5):565–568

Buntrock H ,Reuther T, Prager W, Kerscher M. Efficacy ,safety, and patient satisfaction of a monophasic cohesive polydensified matrix versus a biphasic nonanimal stabilized hyaluronic acid f iller after single injection in nasolabial folds. Dermatol Surg 2013;39(7):1097–1105

Clark CP III. Animal-based hyaluronic acid fillers: scientificand technical considerations. Plast Reconstr Surg. 2007;120 (6, Suppl): 27S–32S.

Colbert SD, Southorn BJ, Brennan PA, Ilankovan V. Perilsof dermal fillers. Br Dent J. 2013;214(7):339–340.

Damrose EJ. Radiographic properties of injected calcium hydrox- ylapatite: potential false positive findings on positron emission tomography. J Laryngol Otol. 2008;122(12):1394–1396.

De Boulle K, Glogau R, Kono T, et al. A review of the metabolism of 1,4-butanediol diglycidyl ether-crosslinked hyaluronic acid dermal fillers. Dermatol Surg. 2013;39(12):1758–1766. doi:10.1111/ dsu.12301 11. Walker K, Basehore BM, Goyal A, Bansal P, Zito PM. Hyaluronic Acid. Treasure Island (FL): StatPearls; 2021.

Dugaret AS, Bertino B, Gauthier B, et al. An innovative method to quantitate tissue integration of hyaluronic acid-based dermal fillers. Skin Res Technol. 2018;24(3):423–431. doi:10.1111/srt.12445.

El-Halaby A, Furtado Araújo MV. Unusual radiographic finding during routine periodontal maintenance: a case report. Tex Dent J. 2014;131(4):297–300.

Flynn TC, Sarazin D, Bezzola A, Terrani C, Micheels P. Comparative histology of intradermal implantation of mono and biphasic hyaluronic acid fillers. Dermatol Surg. 2011;37(5):637–643. doi:10.1111/ j.1524-4725.2010.01852.x

G. Ablon. Understanding how to prevent and treat adverse events of fillers and neuromodulators. Plastic and Reconstructive Surgery, Global Open. 2016; 4912): e1154.

Ginat DT, Schatz CJ. Imaging features of mid face injectable fillers and associated complications. AJNR Am J Neuroradiol. 2013; 34(8):1488–1495.

Ginat DT, Schatz CJ. Imaging of facial fillers: additional insights. AJNR Am J Neuroradiol. 2012;33(11):E140–E141.

Grippaudo FR, Di Girolamo M, Mattei M, Pucci E, Grippaudo C. Diagnosis and management of dermal filler complications in the perioral region. J Cosmet Laser Ther. 2014;16(5):246–252.

Grippaudo FR, Pacilio M, Di Girolamo M, Dierckx RA, Signore A. Radiolabelled white blood cell scintigraphy in the work-up of dermal filler complications. Eur J Nucl Med Mol Imaging. 2013; 40(3):418–425.

J. M. Lee and Y. J. Kim. Foreign body granulomas after the use of dermal fillers: pathophysiology, clinical appearance, histologic features, and treatment. Archives of Plastic Surgery. 2015; 42(2): 232–239.

K. K. Seo. Facial volumization with fillers. Singapore: Springer. 2021;29–83.

Khunmanee S, Jeong Y, Park H. Crosslinking method of hyaluronic-based hydrogel for biomedical applications. J Tissue Eng. 2017;8:2041731417726464. doi:10.1177/2041731417726464.

M. Signorini, S. Liew, H. Sundaram, et al. Global aesthetics con sensus: avoidance and management of complications from hyaluronic acid fillers- evidence- and opinion- based review and consensus rec ommendations. Plastic and Reconstructive Surgery. 2016; 137(6): 961e–971e.

Mero A, Campisi M. Hyaluronic acid bioconjugates for the delivery of bioactive molecules. Polymers. 2014; 6 (2):346–369.

Merola F, Scrima M, Melito C, et al. A novel animal model for residence time evaluation of injectable hyaluronic acid-based fillers using high-frequency ultrasound-based approach. Clin Cosmet Investig Dermatol. 2018;11:339–346. doi:10.2147/CCID.S156740.

Micheels P, Besse S, Flynn TC, Sarazin D, Elbaz Y. Superficial dermal injection of hyaluronic acid soft tissue fillers: comparative ultrasound study. Dermatol Surg. 2012;38(7 Pt 2):1162–1169. doi:10.1111/j.1524-4725.2012.02471.x

Mochizuki M, Aoi N, Gonda K, Hirabayashi S, Komuro Y. Evaluation of the In Vivo Kinetics and Biostimulatory Effects of Subcutaneously Injected Hyaluronic Acid Filler. Plast Reconstr Surg. 2018;142(1):112–121.

Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: a key molecule in skin aging. Dermatoendocrinol. 2012;4(3):253–258. doi:10.4161/derm.21923.

Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol. 2011;64(1):1–34, quiz 35–36.

Rodrigues-Barata AR, Camacho-Martínez FM. Undesirable effects after treatment withdermalfillers.JDrugsDermatol2013;12(4): e59–e62.

Ryu HJ, Kwak SS, Rhee CH, Yang GH, Yun HY, Kang WH. ModelBased prediction to evaluate residence time of hyaluronic acid based dermal fillers. Pharmaceutics. 2021;13:2. doi:10.3390/ pharmaceutics13020133.

Segura S, Anthonioz L, Fuchez F, Herbage B. A complete range of hyaluronic acid filler with distinctive physical properties specifically designed for optimal tissue adaptations. J Drugs Dermatol. 2012;11(1 Suppl):5-8.

Song JE, Kim MJ, Yoon H, et al. Effect of hyaluronic acid (HA) in a HA/PLGA scaffold on annulus fibrosus regeneration: in vivo tests. Macromolecular Res. 2013;21(10):1075–1082. doi:10.1007/s13233-013-1137.

Stern R, Asari AA, Sugahara KN. Hyaluronan fragments: an information-rich system. Eur J Cell Biol. 2006;85(8):699-715

Valachova K, Svik K, Biro C, et al. Impact of Ergothioneine, hercynine, and histidine on oxidative degradation of hyaluronan and wound healing. Polymers. 2020;13(1): 8-12.

Zamboni F, Keays M, Hayes S, et al. Enhanced cell viability in hyaluronic acid coated poly(lactic-co-glycolic acid) porous scaffolds within microfluidic channels. Int J Pharm. 2017;532(1):595–602. doi:10.1016/j.ijpharm.2017.09.053.

Zamboni F, Okoroafor C, Ryan MP, et al. On the bacteriostatic activity of hyaluronic acid composite films. Carbohydr Polym. 2021;260:117803. doi:10.1016/j.carbpol.2021.117803.

Zamboni F, Ryan E, Culebras M, Collins MN. Labile crosslinked hyaluronic acid via urethane formation using bis(beta-isocyanatoethyl) disulphide with tuneable physicochemical and immunomodulatory properties. Carbohydr Polymers. 2020;245:116501. doi:10.1016/j.carbpol.2020.116501.