

Hyaluronic Acid Dermal Fillers: Safety and Efficacy for the Treatment of Wrinkles, Aging Skin, Body Sculpturing and Medical Conditions

Uwe Wollina¹ and Alberto Goldman²

¹Department of Dermatology and Allergology, Hospital Dresden-Friedrichstadt, Academic Teaching Hospital of the Technical University of Dresden, Friedrichstrasse 41, 01067 Dresden, Germany. ²Clinica Goldman, Av. Augusto Meyer 163 conj. 1203, Porto Alegre, RS 90550-110, Brazil. Corresponding author email: wollina-uw@khdf.de

Abstract: Hyaluronic acid (HA) is a linear naturally occurring polysaccharide formed from repeating disaccharide units of N-acetyl-D-glucosamine and D-glucuronate. HA is omnipresent in the human body but highest amounts are found in soft connective tissues. HA is involved in several key processes, including wound repair, regeneration, and matrix organization. To increase stability, modifications of HA like various crosslinking substances and technologies have been developed. In recent years, most HA-fillers are of bacterial origin which ensures very low protein contaminations. HA fillers are temporary fillers, which can easily be digested by hyaluronidase, usually lasting for 6 to 9 months. They are safe for volumizing procedures when used with the appropriate technique and indications. Various types of clinical application are discussed. Best data are available for facial rejuvenation, in particular for nasolabial folds and the periocular region. Combining HA dermal fillers with other techniques allows an individualized treatment. In addition, HA fillers are useful to improve medical conditions such as scars and HIV-associated lipodystrophy as well. This review will provide an overview on the potential of this class of filler substances.

Keywords: hyaluronic acid, dermal fillers, soft tissue, matrix regeneration, aging skin, scars, sculpturing

Clinical Medicine Reviews in Therapeutics 2011;3 107–121

doi: [10.4137/CMRT.S6928](https://doi.org/10.4137/CMRT.S6928)

This article is available from <http://www.la-press.com>.

© Libertas Academica Ltd.



Introduction

Although mass media debate about the benefits of aesthetic surgery, nonsurgical procedures account for the majority of procedures performed. In the USA, there was a 48% growth from 2000 to 2008 in nonsurgical treatments for women, and 64% for men. Clearly there is a rising trend for nonsurgical treatments, including the use of hyaluronic acid (HA) fillers.¹

HA (syn.—hyaluronan) is a linear naturally occurring polysaccharide formed from repeating disaccharide units of N-acetyl-D-glucosamine and D-glucuronate. HA is an extraordinarily versatile glycosaminoglycan that has a very high molar mass and possesses interesting visco-elastic properties based on its polymeric and polyelectrolyte characteristics. HA is omnipresent in the human body, occurring in almost all biological fluids and tissues, although the highest amounts of HA are found in the extracellular matrix of soft connective tissues like skin. HA is involved in several key processes, including cell signalling, wound repair and regeneration, morphogenesis, and matrix organization.²

Mechanisms of Action, Metabolism and Pharmacokinetic Profile

Naturally occurring HA is rapidly broken down by hyaluronidase with a half-life of about 12 hours and eliminated through the lymphatics and by the hepatic metabolism to carbon dioxide and water. By cross-linking HA filler achieve an *in vivo* life span of 6 to 9 (to 12) months.

The use of HA is particularly attractive for soft-tissue augmentation, because it is hydrophilic and a normal extracellular component of skin. The hydrophilic nature allows HA gaining larger volumes relative to their mass. Its allergenic potential seems to be very low compared to other fillers using extracellular matrix components like collagen. Therefore, it can be used without skin testing.³⁻⁵

There is number of factors that impact HA filler persistence like HA concentration, percentage of cross-linkage, type of cross-linkage, water binding capacity, and injection technique. Monophasic gels seem to be more stable compared to diphasic gels.

To improve longevity, manufacturers use various agents and technologies to cross-link the HA. As a result, the final proportion of cross-linked HA and the degree of cross-linking has much influence on physical characteristics of the commercial product.⁶

Recent study results suggest that increased concentration of HA prolongs persistence. If all other factors are the comparable, the HA product with the highest degree of cross-linking will delay degradation by enzymes and free radicals. The cross-linking agents also have an impact on connective tissue reaction to HA fillers.³⁻⁵

Injection technique can play a role in longevity of the volumizing effect. Injection into the deep dermis has been shown to increase *de novo* collagen synthesis, hypothesized to be the result of fibroblast stretching. It is assumed that novel collagen synthesis replaces the HA after HA degradation which results in longer-lasting volumizing effects.³⁻⁵

Histologic evaluation of skin biopsies demonstrated an increased collagen deposition around the filler. Immunostaining for prolyl-4-hydroxylase and the C-terminal and N-terminal epitopes of type I procollagen was increased. Furthermore, gene expression for types I and III procollagen and several profibrotic growth factors were up-regulated for several weeks compared with controls.⁷

The number of FDA-approved fillers in the United States has grown very rapidly.⁸ The situation in other parts of the world is following the same trend. Some examples are listed in Table 1.

HA filler differ in their manufacturing processes, viscosity, hardness, cohesivity, HA concentration, gel-to-fluid ratio, HA gel concentration, degree of HA modification, percentage of cross-linking, swelling, modulus, and particle size, ease of injection, and ideal uses. By careful selection of filler type for the patient's needs and the anatomical situation it is possible to provide aesthetic solutions that meet patient expectations.⁹⁻¹⁴

Recent Developments

Recently a novel, biocompatible, and nontoxic HA filler was developed by a new cross-linking technology. HA hydrogels were prepared by direct amide bond formation between the carboxyl groups of HA and hexamethylenediamine (HMDA) with an optimized carboxyl group modification for effective tissue augmentation. The filler was studied in a wrinkled mouse model. By image analysis volumizing effects of HA-HDMA were compared with Restylane® (Q-med, Uppsala, Sweden), adipic acid dihydrazide grafted HA (HA-ADH) hydrogels, and negative controls. The HA-HMDA hydrogels exhibited the best tissue augmentation effect being stable for more than three months. Histologic

**Table 1.** Characterization of some HA fillers.

Product	Esthélio belotero basic, intense	Captique	Glytone	Hylaform, hylaform plus	Juvéderm ultra, ultra plus	Prevelle, puragen	Restylane, perlane	Teosyal deep lines, ultimate
company	Anteis; Merz	Genzyme Biosurgery	Pierre Fabre	Genzyme Biosurgery	Allergan	Mentor	Q-Med	Teoxane
Source of HA	Bacterial	Bacterial	Bacterial	Avian	Bacterial	Bacterial	Bacterial	Bacterial
Crosslinking agent	BDDE	DVS	BDDE	DVS	BDDE	DVS; DEO	BDDE	BDDE
HA concentration (mg/mL)	22.5; 25.5	5.5	20–23	5.5	24; 26	4.5–6.5; 20	20	25; 22
Gel particle size (µm)	–	500	–	500; 700	–	350, 250	300; 650	–
Gel particle count/mL	–	?	–	?	–	?	10 ⁵ ; 10 ⁴	–
Tan δ*	0.70; ?	?	?	0.14; 0.11	0.40; 0.26	?, 0.24	0.28; 0.30	?
Monophasic gels	+	–	+	–	+	–	–	+
Durability (months)	6–12	6–9	6–9	3–4	6–12	3–4, 6–9	6–12	6–12

Notes: *Tan δ represents a rheologic parameter: δ = viscous modulus divided by elastic modulus. Lower tan δ corresponds to a stiffer gel with longer persistence.

Adapted from Kablik et al 2009; Falcone and Berg 2009; Gold 2007.^{6,12,13}

Abbreviations : BDDE, 1,4-butanediol diglycidyl ether; DVS, divinyl sulphone; DEO, 2, 7, 8-diepoxyoctane.

investigations demonstrated increased dermal thickness and dermal collagen density after treatment with HA-HMDA hydrogels for 12 weeks.¹⁵

Histologic Localization of HA-Filler

The position of the filler within the skin is one determinant of the end cosmetic result. To determine the anatomic location of injected HA filler within nasolabial fold skin, histologic investigations were performed in 16 adult patients undergoing Mohs micrographic surgery for basal cell carcinoma. All 16 patients showed HA filler localized to the subcutis. In addition 9 of 16 samples demonstrated some HA in the deep dermis. The results suggest that dermal localization of HA filler products is not only not required for an excellent cosmetic result but current injection technique will place the majority of HA subcutaneously.¹⁶

Tools for Measurement of Patients-Reported Outcome

Patient-reported outcomes data are limited after injectable soft tissue filler treatment. Patient-reported outcome measures (PROMs) are becoming integral to medical practices. Understanding the patient's expectations,

experience and satisfaction with treatment is essential to continue to provide excellent care to facial aesthetic patients. Facial Injectables: Longevity, Late and Early Reactions and Satisfaction Questionnaire (FILLERS-Q) is a new tool in assessing patient response to facial injections of soft tissue fillers. The questionnaire captures patient demographics, satisfaction with treatment, procedure-related events, impact on relationships, and economic considerations.¹⁷ Further studies will evaluate the usefulness of such a tool to improve techniques and products for facial sculpturing.

Clinical Studies

Facial Rejuvenation and Treatment of Wrinkles

Injection Techniques

There are different injection techniques: The threading injection, that delivers the filler along the defect when the needle is extracted, needs fewer punctures. The multiple puncture technique placed beads of filler. For more advanced users, anterograde or push-ahead injection is another option. Slower injection speed is generally recommended.

Variants of these techniques are cross-hatching, fanning, tunnelling, feathering and tenting. Before and after injection, application of cold compresses will reduce pain, swelling and tenderness.¹⁸

As discussed above, filler placement usually is subcutaneously. Intramuscular filler placement should be avoided with the exception of monophasic HA.

Temple Rejuvenation

Temple hollowing with soft tissue volume loss is well recognized in HIV lipoatrophy. Similar changes occur as part of aging, with skeletalization of the orbital rim and clipping of the eyebrow tail.

The treatment of temple volume loss and orbito-facial asymmetry with HA was analyzed in a retrospective, interventional case series ($n = 20$). Patients initially received approximately 1 mL of Perlane® (Q-Med, Uppsala, Sweden) injected into the superficial fascia of each temple. The filler was placed behind the frontozygomatic process to soften the bony contour of the lateral orbital rim. After a mean follow-up of nine months (range: 4 to 14 months) 13 of 16 patients who replied to the questionnaire were very or moderately satisfied. Side effects included mild or moderate discomfort, superficial vein prominence, and localized bruising. The study suggests that HA is effective and safe in temple hollow rejuvenation.¹⁹

Periorbital Rejuvenation

In the aging process, upper periorbits can be divided broadly into two groups. Group 1 is characterized primarily by soft tissue ptosis of the upper eyelid. This condition requires surgical intervention. Group 2 shows volume depletion of the soft tissue and bony resorption of the orbit. This leads to deflation of the upper eyelid as well as sunken, hollow, and skeletonized orbits. Group 2 patients are candidates for volumizing procedures (Fig. 1). In a single center series, 36 group 2 patients were treated with HA

fillers to restore the smooth arc of the upper periorbit. Despite the relatively small volume required (up to 0.6 ml), the upper periorbital aesthetics of the patients were markedly improved in some patients for as long as 3.5 years. No significant morbidities occurred.²⁰

In another trial HA filler (Perlane®) was used as tear-trough filler over an 18-month period. A total of 198 eyes of 100 patients (mean age 47.8 years) were treated, with a mean follow-up of 5.1 months. HA filler was placed preperiosteally, deep to orbicularis, and anterior to the inferior orbital rim. The mean filler volume was 0.6 ml per eye. The most common side effects were bruising (75%), swelling (26%), Tyndall effect with blue discoloration (4%), and lumpiness (33%). Of these patients 85% were marked or moderate satisfied, 5% were ambivalent, and 10% were dissatisfied.²¹

A prospective, blinded case series used three-dimensional imaging to quantify augmentation and long-term duration of effect HA filler in the tear trough ($n = 20$). The average augmentation was 0.21 cm³ per site. Average maintenance of effect for patients at the final follow-up visit was 85 percent during an average follow-up of 14.4 months.²²

HA filler can also be used for upper eyelids. In a consecutive, retrospective, interventional case series, standard serial puncture injections with pre-periosteal placement of filler were administered at the superior orbital rim. Twenty-seven patients were included with a mean follow-up of 13 months. Photographic assessment showed improved static upper eyelid contour in 23 patients (85%), little change in 3 patients (11%), and deterioration in one patient. Twenty-six patients (96%) were satisfied with the treatment. Most common side effects were mild bruising and swelling but no discoloration or lumpiness. HA filler are effective in rejuvenating the upper eyelid and are particularly successful in medial and generalized upper eyelid hollowing, or significant postblepharoplasty upper eyelid show.²³

Upper eyelid margin asymmetry in cases of relative retraction can be an indication for HA-filler. In a retrospective study of 8 patients digital photographs were used to quantitatively assess outcomes by comparing pretreatment and posttreatment differences between marginal reflex distance (MRD1) in the right and left eyelids. The average volume injected in the upper eyelid was 0.2 ml (range, 0.1–0.4 ml). One of 8 patients was injected bilaterally, two patients requested repeat injection for undercorrection. Average follow-up

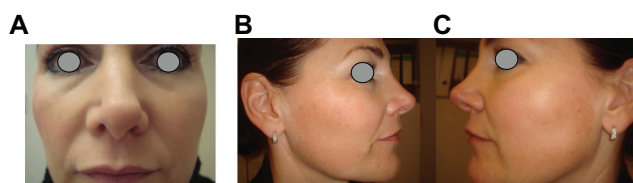


Figure 1. 46-year-old female. **A)** Before and **B, C)** after liquid lift with Belotero Intense® (malar region). Improvement of tear-trough and nasolabial folds.

was 5.7 months (range, 2–12 months). The mean pretreatment MRD1 difference of 1.53 mm improved statistically posttreatment with an MRD1 difference of 0.70 mm. The effect was still obvious in all patients at 8 months' follow-up. This pilot study suggests that upper eyelid injection with HA filler may be an effective nonsurgical alternative to improve upper eyelid margin asymmetry.²⁴

Subdermal support of the lateral two-thirds of the brow with HA filler results in a non-surgical brow-lift. The appearance is softer and more relaxed compared to surgical overcorrections.²⁵

Facial Sculpturing: Malar and Cheek Area

The correction of volume loss has become an important part of facial rejuvenation treatments, particularly in the midface region (Figs. 2 and 3). Techniques to date have largely relied on multiple injections, fanning techniques and deep placement of product under muscle or on periosteum. Others have used a single injection of cross-linked hyaluronic acid at the subdermal level and above the muscle. The technique approaches midface rejuvenation with reference to both the bony skeleton and the medial malar fat compartment. After appropriately marking the skin, the filler is placed using a blunt cannula reducing thereby the risk of bruising. The treatment achieves satisfactory volume correction, enhancing the sharp cheek bones and malar fullness typical of an attractive adult face. The approach is simple, quick, and well tolerated by the patient and may result in less bruising than deeper techniques.²⁶

Comparative trials have been performed with Juvéderm Voluma® (Voluma) and Restylane SubQ®

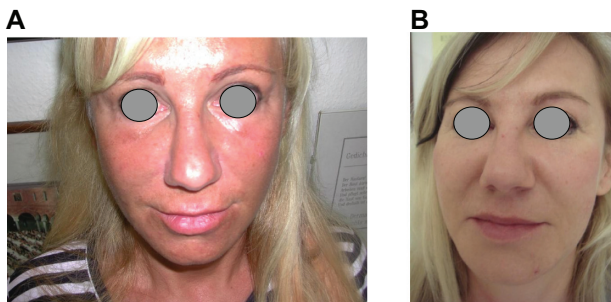


Figure 2. 41-year-old female before and after liquid lift (Juvéderm Voluma®) for the malar region. Improvement of tear-trough, nasolabial folds and upper lip.

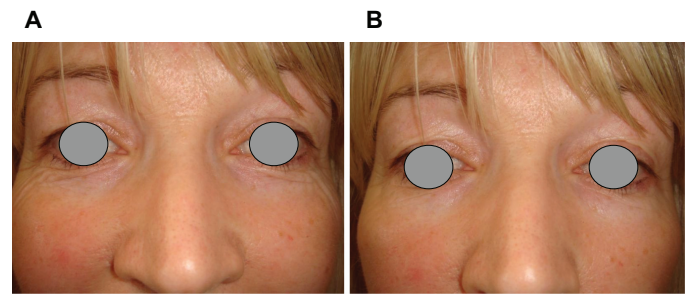


Figure 3. Improvement of tear trough, lower lids and cheekbones with a 1 mL Belotero Basic® in a 42-year-old female. **A)** Before and **B)** after treatment.

(Restylane). Voluma HA filler was used in 84 adult patients (mean age 51 years) who had received Restylane previously. The mean total volume of Voluma injected was 2.73 mL/patient to both sides of the face, specifically in the malar and chin areas. The majority of patients (98%) and physicians (98%) rated the aesthetic effect of Voluma as improved. Injectors rated Voluma as better than previous Restylane use in 69.1% of patients, and preference for Voluma was expressed in 61% of patients. Treatment was well tolerated.²⁷

In a multicentre trial Juvéderm Voluma® was used for correction of moderate volume loss, mainly of malar and cheek area. Fifteen physicians and 70 patients participated. On the Global Aesthetic Improvement Scale, 88% and 76% of the treatments were rated very much improved or much improved by physicians and patients, respectively. Transient injection-site adverse events occurred in 24 patients, with bruising as the most common.²⁸

Facial Sculpturing: Nasolabial Folds (NLFs)

NLF augmentation can improve first impression rating by observers. HA filler injections in NLFs were performed in 22 patients. Photographs of the face in a relaxed pose were taken at baseline, optimal correction visit, and 4 weeks after optimal correction. Blinded evaluators completed a survey rating first impression on various measures of success for each photo. At four weeks after the injection, significant improvement was observed in all categories measured: social skills, academic performance, dating success, occupational success, attractiveness, financial success, relationship success, athletic success, and overall first impression.²⁹



Long-term efficacy and the effects of different retreatment schedules for HA filler were evaluated during an 18-month interim analysis of a 30-month multicenter, randomized, evaluator-blinded study. Patients ($n = 75$) with NLFs were randomized to retreatment of one nasolabial fold at 4.5 months and the contralateral fold at 9 months after correction of both folds at the initial visit. Wrinkle Severity Rating Scale scores improved significantly ($P < 0.001$) from baseline. Most patients (97%) responded satisfactorily, and the efficacy of the retreatment schedules did not differ significantly. Adverse events like primarily swelling and bruising occurred in one third of patients.³⁰

Safety and effectiveness of a nonanimal-sourced HA (which uses a cohesive polydensified matrix (CPM) technology [CPMHA]; Esthélis, Anteïs, Switzerland) was evaluated for the treatment of NLFs during an 18-month open-label extension trial. Ninety-five of 118 subjects continued with this optional open-label extension of a split-face, double-blind trial. All subjects received CPMHA in both NLFs at 24 weeks after treatment in this study and were assessed at weeks 32, 48, 72, and 96. Touch-ups were allowed for optimal correction. At all four post-week 24 time points, the severity of the NLFs showed a decrease from baseline on the Wrinkle Severity Rating Scale. The effects persisted in 80% of subjects without repeat treatment for at least one interval of 48 weeks. The HA filler was well tolerated.³¹

Anteïs entered a strategic partnership with Merz Pharma (Frankfurt/M., Germany). The Anteïs portfolio is sold under the brand Belotero by Merz. The monophasic CPMHA filler Belotero (Merz, Germany) has been evaluated in a prospective multicentre trial including 114 adult patients with deep NLF. The mean injected volume was 2 mL per face. After six months 81% of participants showed efficacy, after 9 months the rate was 66%. After six months the tolerability was rated good or better in 109/114 patients. No severe adverse effects were observed. Temporary mild adverse reactions such as redness or swelling after injection were common.³²

Another study evaluated the effectiveness of Juvéderm injectable gel (Juvéderm Ultra®, Juvéderm Ultra Plus®, and Juvéderm 30®) through 1 year after repeat treatment of NLFs that were previously treated

with Juvéderm or Zyplast® 6–9 months prior to the repeat treatment. A total of 80 subjects were enrolled. For the Juvéderm®-treated NLFs in each treatment group, the median injection volume was 1.5–1.6 mL for initial treatment and 0.5–0.6 mL for the repeat treatment. Mean investigator-assigned NLF severity scores improved from moderate to severe at baseline to mild just prior to repeat treatment (>24 weeks) and at 4 weeks after repeat treatment. At 48 weeks post-repeat treatment, the mean NLF scores were mild again, and the majority of subjects were considered responders. Thus, subjects sustained a total of 18–21 months of wrinkle correction with a repeat treatment at 6–9 months and needed substantially less filler (60% less) for repeat treatment than for initial treatment, indicating that retreatment at this time point may be beneficial to patients.³³

Dermal gel extra (DGE) is a new, tightly cross-linked HA-based dermal filler containing lidocaine engineered to resist gel deformation and degradation. DGE has a higher modulus and a higher gel:fluid ratio than other HA fillers. Similar optimal correction was observed with DGE and a non-animal source HA (NASHA) through 9 months in a split face trial for nasolabial folds. The advantage of DGE was that subjects required less volume ($P < 0.001$) and fewer touch-ups ($P = 0.005$) and reported less injection pain ($P < 0.001$) compared with NASHA.³⁴

Rhinoplasty

Using soft tissue fillers to correct postrhinoplasty deformities in the nose is appealing. Fillers are minimally invasive and can potentially help patients who are concerned with the financial expense, anesthesia risk, or downtime generally associated with a surgical intervention. HA filler have most frequently been used for treating nasal deformities. The nasal injection technique must include sub-SMAS placement to eliminate visible or palpable nodularity. Restricting the use of fillers to the nasal dorsum and sidewalls minimizes complications because more adverse events occur after injections to the nasal tip and nasal alae. It is highly recommended that HA treated patients for this indication must be followed closely for complications since HA may occasionally lead infection, thinning of the skin envelope, and necrosis.³⁵



Lips

The youthful face has a soft, full appearance, including the lips. Genetic factors influence the shape of the lip and the ratio between upper and lower lip. Injectable HA fillers can augment and even at times, replace pulling. Subtle lip enhancement and/or lip contouring offers cosmetic enhancement without the cost and recovery time associated with more invasive procedures but the drawback of repeated applications needed over time.³⁶

Surprisingly, no controlled randomized, prospective trials are available for lip treatment although lip augmentation is a very common indication in practise. Surgical repair of cleft lip, while correcting deformity and dysfunction, may leave residual cosmetic imperfections. The resultant asymmetry and low volume of the upper lip was treated by HA filler to restore symmetry and achieve an augmented volume. The authors obtained a symmetric correction and aesthetically pleasing volume augmentation in the affected lip lasting for approximately 4 months. For patients who have endured multiple corrective surgeries, this is a less invasive way to improve their aesthetic outcome.³⁷

Melolabial and Mental Creases

HA fillers are useful for melolabial and mental creases. Although no controlled trials have been published in clinical practise HA filler placement in this area often is combined with botulinum toxin A, laser or medical peelings to obtain better and longer lasting results.^{3-5,38,39}

Earlobes

Cosmetic disfigurement of the earlobe, including laxity and sagging skin, comes with aging. Restoring the earlobe volume is a procedure indicated for patients seeking a youthful facial appearance. Injectable HA is an option for this procedure. A larger-gauge needle allows the introduction of the product under lower pressure, making it easier and faster to fill tight areas.⁴⁰

Restylane Perlane® has been used for volumizing earlobes in a diagonal linear or feathering injection technique with excellent results. For patients with an enlarged earlobe piercing due to skin aging, a circular microdepot technique is capable to improve appearance and stabilize the piercing hole.⁴¹

Other Applications

Scar treatment

The treatment of atrophic scars is difficult. Dermal HA filler materials provide a simple alternative with immediate but temporary results. In a study 12 patients with facial atrophic scars caused by acne vulgaris, dog bite, piercing, basal cell carcinoma and leishmaniasis were treated with HA filler Esthélics®. The injection technique was linear threading, serial puncture or a combination of both. Physicians rated the results as moderate (27%), good (57%) and excellent (17%) one month after the injection. Patients evaluated the cosmetic improvement as good (42%) or excellent (58%) at the same time. Side effects included mild to moderate pain during the injection and mild erythema immediately after injection, which spontaneously resolved within few hours. The best results were observed in patients with more deforming atrophic scars such as surgical scars or scars after trauma.⁴²

HIV-associated facial lipoatrophy

Human immunodeficiency virus (HIV)-associated facial lipoatrophy (FLA) represents a common and highly stigmatizing side effect of retroviral therapy. By causing loss of subcutaneous adipose tissue mainly in the cheek, temple and periocular area, FLA can significantly affect the patient's quality of life, both physically and psychologically. A limited quantity of data has been published on various filling substances for the management of FLA.

In a clinical trial 20 HIV patients received injections of Restylane SubQ®. Refill treatment was offered twice, ie, at 12 and 24 months. Treatment effects were evaluated using ultrasound, the Global Aesthetic Improvement Scale, visual analogue scale (VAS) and the Rosenberg self-esteem scale. Seventeen patients remained at 36 months. During treatment ultrasound revealed a mean total cutaneous thickness increased from 6 mm at baseline to 12 mm after 3 years. Response defined by total cutaneous thickness > 10 mm was 70%. Fifteen patients classified their facial appearance as very much or moderately improved. VAS increased and higher self-esteem scores were reported by patients. The spectrum of side effects included local swelling and tenderness after injection and persistent granulomas

after treatment. Granulomas were removed effectively with hyaluronidase injections.⁴³ A similar experience was documented for monophasic volumizing filler in 23 patients with HIV-associated FLA, but granuloma formation was not a problem.^{44,45}

Steroid atrophy

The potential use of HA filler for steroid atrophy has been documented in a single case report.⁴⁶

Hand rejuvenation

Aging hands are an often overlooked problem in aesthetic medicine. Although the hands age at the same rate as the face, the aging process differs and requires a combination treatment approach for optimal rejuvenation. Thinning of the dermis and subcutaneous fat can lead to a skeletal appearance of the hands, with prominent veins and bulging tendons. The combination approach addresses all of these issues, employing lasers, intense pulsed light devices, peels etc. but dermal fillers play an important role in augmentation.^{47,48}

The subcutaneous tissue of the dorsal hand has a particular anatomy. It is divided into three fatty laminae separated by fascia layers with multiple vessel-containing septal perforations. An injection technique that addresses the fatty laminae and the perforating septa may yield improved and consistent rejuvenation results. Intravascular injections need to be avoided by this technique—as in the face.⁴⁹

In a randomized study 10 female patients were treated with either HA (Restylane®, Medicis Aesthetics Inc.) or collagen (Cosmoplast®, Inamed Aesthetics) for soft tissue augmentation of the dorsal hands. They received 1.4 mL of HA or 2.0 mL collagen and hands were scored blinded for clearance of veins. Outcome analysis showed a superior efficacy of the HA filler to collagen. Patient satisfaction, however, was not significantly different.⁵⁰

The subdermal injection into alternate interphalangeal spaces of dorsal hands can be performed by a long blunt 18 gauge needle in feathering technique or by tenting technique using a 30 gauge needle.⁵¹ Larger studies on use of HA-fillers for hand rejuvenation are missing. A different approach for hand rejuvenation is microdroplet injection (Fig. 4). A single-center, prospective, randomized study evaluated the effects of intradermal microdroplet placement of Restylane Vital® and Teosyal Meso® (Teoxane; Switzerland)

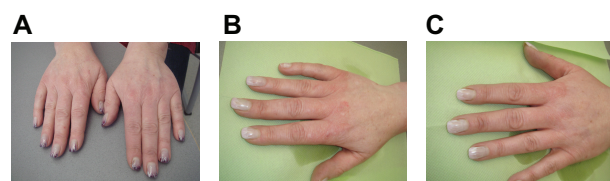


Figure 4. 32-year-old female with combined HA-filler (Glytone 3) and botulinum toxin A (Boccuture®; Merz) for frown lines. **A)** before, **B)** two weeks after filler 1 ml botulinum toxin (50 U). Note the relaxed appearance and the slight brow lift.

in 15 volunteers. Three sessions of injections with 30 gauge needles were performed at weeks 0, 4 and 8 after pretreatment with EMLA® cream since multiple injections are necessary. In this trial Restylane Vital® was superior to the non-stabilized HA filler in improvement of skin surface roughness, gross skin elasticity and stratum corneum hydration. More important is the clinical assessment. At week 12 stabilized HA filler Restylane Vital® was scored significantly better.⁵²

Foot rejuvenation

HA filler can be used for the dorsal part of feet in tenting technique with slow injection speed. Becker-Wegerich (2008) recommended the use of Restylane Vital® in a frequency of once every 4 to 8 months.⁴¹

Genital procedures

Despite the debates on penile girth enhancement, demands for enhancement are increasing in some parts of the world. In a South Korean study 50 patients with subjective small penis were treated by injections of Restylane Sub-Q® into the fascia layer of penile body using a 21 gauge cannula followed by massage with a roller. The mean injected volume was 20.6 cm³. Of the 41 patients who completed 18 months follow-up maximal circumference increased from 7.5 cm to 11.3. The enhancement of penile girth was stable from one month after injection to the end of follow-up.

There were no asymmetries, inflammation or serious adverse reactions observed.⁵³ Longer follow-up data are yet not been published.

Kwak et al (2008) created glans penis augmentation by injectable HA gel and reported the 6-month result for premature ejaculation. In 38 patients, long-term effects of 5 years were compared to those of 6 months in terms of residual volume of implants and efficacy on premature ejaculation. Maximal glandular circumference measured by tapeline significantly decreased by 15%.

Intravaginal ejaculatory latency time and vibratory threshold decreased after primary treatment but were still better than before treatment after 5 years. This effect translates into satisfactions rate of 76% for patients and 63% for partners. There was no serious adverse reaction in this study although there is a potential of accidental intravascular injection.⁵⁴

Combined Treatments

Combined procedures often are the best way for an individualized treatment of the ageing face. Because of complementary actions, it is common for HA and botulinum toxin A (BoNT) to be used in the same anatomical sites to optimize outcomes, either administered consecutively at one visit or at two separate visits (Fig. 5).

A recent trial investigated BoNT, HA filler, and combined BoNT and HA filler treatment for lower face rejuvenation. A total of 95 middle-aged female patients were randomized into the three treatment arms, ie, 24-mg/mL HA filler alone ($n = 30$), BoNT alone ($n = 30$), or the combination ($n = 30$). All treatments resulted in significant improvements from baseline. Filler or combined treatments were rated better than BoNT alone by patients and investigators. Participant-rated severity of treatment-related reactions was mainly mild and transient.⁵⁵

Kenner (2010) used HA filler and BoNT in the same syringe at the same time to rejuvenate the upper face. The author concluded that concomitant administration resulted in excellent clinical outcome. His experience argued for increased patient experience by allowing

the use of small-gauge needles and decreasing the number of needle sticks.⁵⁶

On the other hand, the combination of the two products in one syringe can cause problems: a) the exact dosing and placement of BoNT is not easy, since the diffusion may be affected and b) the site of injection of BoNT is not always overlapping with the site of HA filler injection. In some countries mixing two products is considered as a new drug (and in contrast to dermal fillers, botulinum toxin is a registered drug). This has legal consequences.

HA fillers and laser/light procedures have become increasingly popular for noninvasive facial rejuvenation in many cosmetic practices. In two studies there were no statistically significant differences between wrinkle severity or global aesthetic scores for HA gel implantation alone and HA gel with laser/radiofrequency (RF)/intense pulsed light (IPL) treatment at any time point. In a small sample, histologic changes were not apparent after laser/RF/IPL treatment.^{57,58}

Facial rejuvenation is a significant process involved in restoring youthfulness. The introduction of less invasive procedures has increased acceptance of such procedures. Often a combination of different techniques allows individualized treatment with optimal outcomes. Furthermore, this leads to a natural look without a significant downtime.³⁻⁵

Safety and Adverse Effects

Contraindications and limitations

HA fillers should not be used in patients known to be allergic to any ingredient of the filler product. In contrast to collagen filler, testing before treatment is not necessary.

In patients with autoimmune disease and/or immunosuppressive treatment filler should be used only with great caution.

Patients with bleeding disorders or medical drugs that interfere with blood coagulation have a high risk for bruising and hematoma formation and should therefore not be treated with fillers, especially not with deep filler injections.

Injections are contraindicated when the patient suffers from acute infections (eg, herpes, pyoderma etc.), fever or uncontrolled metabolic disorders like diabetes. On the other hand, there are no scientific data that suggest an increased risk of herpes infections by HA filler augmentation.

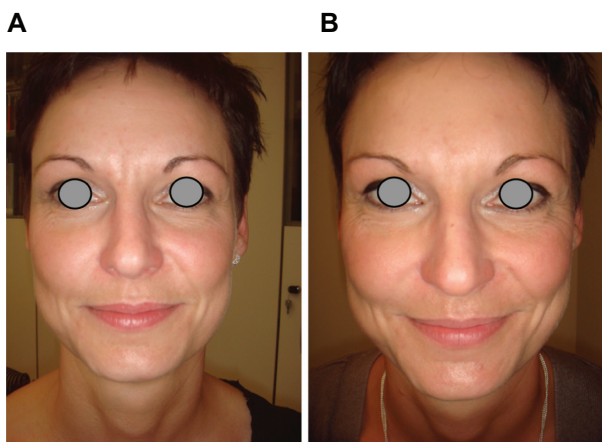


Figure 5. 46-year-old female. Hand rejuvenation with multiple minidrop-let injections (Restylane Vital Light®) **A**) before and **B**) for weeks after a single application of 2 mL HA. Mild improvement suggests the need for repeated treatments.



During pregnancy and lactation filler injection is contraindicated although no adverse effects for the unborn child have been reported yet. Patients who suffer from psychiatric diseases or body dysmorphic disorder should not be treated with dermal fillers.

Since filler injection is a minimally invasive procedure, the risks are lower than of surgery. Nevertheless, the hygienic measures including skin disinfection and sterile equipment are comparable.³⁻⁵

Pain management

Effective pain management is an important component of aesthetic procedures. Consensus guidelines developed for the use of HA fillers describe the use of cooling the skin to reduce patient discomfort during injection. The vasoconstrictive effects of cold may diminish ecchymosis and swelling at the site. However, the effect of applying ice or cooled air is unpredictable because these modalities do not deliver precise temperature, which may result in cold burn or insufficient effect to targeted areas. In an open-label, randomized, single-blinded, split-face trial the extent to which applying a spot cooling device reduces patient discomfort and ecchymoses in dermal filler procedure was analyzed. Twenty adult subjects with moderate and severe NLFs were included in this study. The use of a topical cooling system (35 degrees F; 20 seconds) resulted in a mean pain reduction between 61% (immediately after injection) and 70% (one hour after injection). Additionally, use of the cooling system reduced ecchymosis by 80% to 89% in the first three hours postinjection. Future studies are needed comparing the use of topical anesthetics to a cooling system for the reduction of pain and ecchymosis.⁵⁹

New formulations of HA filler contain lidocaine. In a randomized study Juvéderm injectable gel with lidocaine (denoted as JUV + L) and Juvéderm® injectable gel without lidocaine (denoted as JUV) were evaluated with respect to procedural pain scores in subjects undergoing NLF augmentation. JUV + L was scored to be less or slightly less painful than JUV by 93% of subjects treated. Improvement in NLF severity was not different.⁶⁰

Evaluation of pain at the injection site during and after the injection of Prevelle SILK® (with lidocaine) or Captique® (without lidocaine) was performed in a patient-blinded, prospective, randomized, split-face design trial (n = 45). There was

more than 50% less pain associated with the HA filler with lidocaine than with the same filler without lidocaine especially during injection. The outcome was not different.⁶¹

A single-centered, double-blinded, randomized, with-in patient trial, compared patient comfort when receiving HA injections versus injections of HA mixed with lidocaine hydrochloride 2% (HA + L). Eighteen females were enrolled and completed the study. The average pain rating was significantly less when HA + L was administered as reported by participants and blinded investigators. The addition of lidocaine to HA fillers did not affect longevity during 6 months of follow-up.⁶²

In a larger study, 60 subjects were enrolled in a randomized, double-blind, split-face trial of HA and HA + L for NLF correction. HA + L resulted in pain relief in 95% of patients at the end of injection without altering the safety.^{63,64}

Adverse effects

HA filler use, user groups, and indications have expanded significantly in the past several years. This group of fillers is extremely safe in experienced hands. Complications are infrequent but can be devastating. There can be no substitution for recognized and specific training. Prompt recognition and proper treatment of serious complication can moderate and even prevent serious sequelae.⁶⁵

Acute adverse effects

The most common side effects include swelling, redness, and tenderness at the injection site seen in 70%–90% of patients. Bruising, itching and pain are seen in 30%–60% of patients.⁶⁶ These effects are mostly mild and temporary. Another side effect is a bluish discoloration known as the Tyndall effect, when injections are placed too superficial. Hypersensitivity has rarely been reported with HA fillers.

While biodegradable fillers offer the least risk for the patient compared with permanent fillers, location, allergic reactions, skin necrosis, and infection are all serious complications that must be considered before performing soft tissue augmentation with any approved dermal filler.⁶⁷

A blinded, prospective, randomized subject and evaluator study was conducted at 17 sites in the United States with 248 subjects enrolled treated with

HA fillers. Safety data of large-particle HA filler and small-particle HA filler were collected. Both the fanning injection technique and a faster rate of injection are major risk factors for the increase in incidence of adverse experiences.⁶⁸ Other studies failed to substantiate these findings.⁶⁹

The most devastating acute adverse effects are seen by accidental intravascular injection. There are some facial areas with an increased risk, ie, the forehead, skin within the orbital rim (upper and lower eyelids) and the alae nasi. Blunt cannulas, low volumes and slow injection speed are some preventive measure when no-go areas for fillers are respected.^{70,71} Antihistamines or oral corticosteroids may be used to prevent acute redness and swelling after HA injection.⁷²

The materials used for cosmetic procedures by physicians as well as illegally by non-medical personnel can cause non-thrombotic pulmonary embolism (NTPE). A woman developed acute respiratory failure after an illegal cosmetic vaginal procedure using HA filler by an unlicensed medical practitioner on the day of symptom onset. Histopathological examination of a video-assisted thoracoscopic lung biopsy specimen showed a granulomatous foreign body reaction with multinucleated giant cells around amorphous basophilic materials in the pulmonary vessels and lung parenchyma, suggesting NTPE by HA.⁷³

Delayed adverse reactions

Late or delayed granulomatous foreign-body reactions have been seen rarely with HA fillers.⁶⁶ They might occur months or even years after injection. As microbial agents have been associated with late adverse effects related to fillers antibiotic treatment has been envisaged. On the other hand, HA filler did not show chemoattractive properties or stimulate bacterial growth in experimental settings.⁷⁴ Further studies are needed to better understand the mechanism leading to granuloma formation.

To remove granulomas caused by HA filler injection hyaluronidase is available, surgical excision is rarely necessary in contrast to permanent fillers. Hyaluronidase cleaves HA within 24 hours. However, adverse reactions to hyaluronidase such as allergic reactions have been reported. Patient should be informed about that before treatment (Table 2).⁷⁵ Immune reactions might be responsible for delayed adverse affects to filler. Production of low levels of proinflammatory

cytokines like interferon-gamma in vitro may cause low-grade inflammation in vivo resulting in T cell activation.⁷⁶ Corticosteroid injections are used to solve inflammatory HA-granulomas.⁷²

Although lidocaine is effective in pain reduction, it might be responsible for adverse reactions in some patients. Three patients developed adverse reactions including persistent swelling, pain, and nodule formation. Two of the three patients' abscesses were cultured for aerobic and anaerobic bacteria and mycobacteria but remained negative. The effects subsided only after the product had been removed. Two of these patients were subsequently treated with other HA-derived dermal fillers (not containing lidocaine) without adverse events.⁷⁷ On the other side, there was no direct evidence for a type I or IV allergic reaction to lidocaine. In case of abscess formation, surgery is needed (incision, drainage or expression).⁷⁷

Taufig et al (2009) investigated 11 non-permanent dermal fillers in an in vivo study. They injected small volumes (0.2 mL) into abdominal folds before surgical resection and evaluated the inflammatory reaction by histopathology in four patients for 30 days. They found a cellular immune reaction in nine fillers. In case of monophasic HA (Belotero Basic® and Belotero Intense®; Merz) no immune reaction was observed. This could argue for a better tolerability of this HA filler type, although the number of patients was small and various anatomic regions might react different to implants.⁷⁸

A new resorbable filler, Matridex®, became commercially available during the last years with scarce evidence regarding side effects. A 43-year-old woman complained of multiple, painful, reddish, nonulcerated, hard nodules on both cheeks and periorcular regions four weeks after Matridex® injection.⁷⁹ Another patient developed a delayed inflammatory reaction to an injection of Matridex in the glabellar fold five weeks after the procedure that lasted more than a year.⁸⁰ Based on histopathologic investigations filamentous particles and the spherical particles of dextranomer microspheres have been suspected as being responsive for the sterile inflammatory reaction.⁷⁹

For the glabellar region, severe partly vascular adverse events have been reported after treatment with injectable fillers. Data from the Injectable Filler Safety Study, a German-based registry for those reactions, identified 40 patients. All patients were female,

**Table 2.** Recommendations for the use of hyaluronidase (according to Rzany et al⁷⁵).

Useful information for the patient before treatment:	<ul style="list-style-type: none"> – Hyaluronidase is used off-label for filler removal – Adverse reactions may occur but are seen rarely – Skin tests do not totally exclude such rare adverse effects
Contraindications:	<ul style="list-style-type: none"> – Known allergies to animal proteins – Previous adverse reactions to hyaluronidase
Indications:	<ul style="list-style-type: none"> – Correction of overtreatment – Treatment of Tyndall discoloration – Digestion of nodules
Dilution:	<ul style="list-style-type: none"> – Neither preservatives, nor lidocaine or epinephrine have been shown to improve effect – Dilute 150 U hyaluronidase with 1 mL 0.9% saline
Injection:	<ul style="list-style-type: none"> – Use a 30 gauge needle for superficial and a 27 gauge needle for deeper depots – Keep volumes per injection low, ie, 0.05 to 0.1 mL (ie, 7.5 to 15 U hyaluronidase) – Inject into the nodule; if the nodule is very superficial then inject beneath
Precautions:	<ul style="list-style-type: none"> – Do not inject into areas where botulinum toxin had been injected the last 48 h since hyaluronidase is a spreading factor – Hyaluronidase does not affect filler types other than HA filler
Available products in Europe:	<ul style="list-style-type: none"> – Desinfital (Aesthetic Dermal, UK): 1500 U per vial (Ovine origin) – Hylase Dessau (Riemser Arzneimittel AG, Germany): 150 U, 300 U, or 1500 U per vial (Bovine origin, without preservatives)

with an average age of 52.3. Among those 10 patients were treated with various HA fillers. Vascular complications with necrosis and ulceration were rare and not related to pure HA products.⁸¹

Patients with chronic hepatitis C have a higher risk of interferon-induced sarcoidosis. Physicians must be aware of the risk that a granuloma can develop after a dermal filler injection especially in patients treated with interferon for chronic hepatitis C. These reactions may reveal a systemic sarcoidosis. The authors propose to perform a test for a hepatitis C virus infection before injecting a dermal filler and to inform the patient of this risk in case of a hepatitis C infection that could necessitate an interferon treatment.⁸²

Pigmentary changes may be associated with higher Fitzpatrick skin phototypes. Two prospective studies followed up subjects with Fitzpatrick skin phototypes of IV or higher for 24 weeks after HA filler injections (Juvéderm Ultra[®], Ultra Plus[®], and 30[®]; or Hylaform[®], Hylaform Plus[®], and Captique[®]). For both group there was no case of hypersensitivity, hypertrophic scarring, and no increased incidence of hyperpigmentation or hypopigmentation in non-Caucasian subjects.⁸³

New objective tools for hyaluronic filler efficacy

Many factors contribute to extend productive life in the modern world. Competition makes people worry about physical appearance, mostly in respect to facial and skin aging. This has motivated new developments

in cosmetic dermatology and the need of evaluating patient satisfaction with the new proposed treatments. Satisfaction of a group of 33 middle-aged women treated with HA augmentation of NLFs or lips, was studied combining EEG brain mapping and questionnaire techniques. Poll results showed that patients were feeling well and were satisfied with the results of the aesthetic treatment three months after the procedure. Furthermore, the regression EEG mappings showed patients to be satisfied with their appearance and with the treatment involving similar brain areas.⁸⁴

The use of three-dimensional imagery (Surface Imaging Ltd and Canfield Scientific Vectra 3D Volumetric Analysis System) for evaluating the change in lip volume before and after injection of filler has been investigated.⁸⁵

In a pilot study HA was injected intradermally in the forearm of a young male volunteer. High-resolution magnetic resonance imaging (MRI) scans using a surface antenna were performed just after injection, and after 2, 4 and 9 months. By quantitative MRI the zone of injection was clearly seen. In addition, the diffusion and progressive degradation of the filler agent can be monitored by T(2) measurements over time.⁸⁶

The technique is expensive and time consuming and not suitable for routine. In experimental settings, however, high-resolution MRI may be of great value.

Another non-invasive technique to study filler in vivo is ultrasonography. Thirty-six adult patients

after lip or NFLs filler augmentation, were enrolled for a high-frequency sonography. Twenty patients had an injection of a temporary filler (collagen or HA). Using this technique it was possible to identify the filler at the site of injection. In addition, ultrasonography seems a useful, non-invasive tool for the identification of the type of the filler injected.⁸⁷

The objective of aesthetic treatments is to create a more youthful appearance. There is a strong demand to quantify efficacy of dermal filler injections. Some of the methods are only for scientific approaches. Most commonly used is photography, but standardization and combination with image analysis techniques is a critical issue.

Patients preference

The motivations for patients to undergo aesthetic procedures and the satisfaction with these procedures are quite complex. They seem to be influenced by gender, age, social, religious, cultural and educational factors among others.

An Australian survey among 14,100 females (40–50 year old) seven percent underwent cosmetic surgery. Those females had significantly more health consultations with medical doctors, alternative medicine, chronic medical problems, medications for medical problems with anxiety and sleepless.⁸⁸

The stigmatization of patients seeking aesthetic procedures has not been confirmed by other investigations. In a 2006 survey involving almost 800 US American women (35 to 69 year-old) primary reasons for facial aesthetic procedures were a) to look better, b) feel younger, and c) increase their confidence.⁸⁹ Recently, the “natural look” is a primary goal not only for facial procedures.

We performed a qualitative empirical study in Dresden including 53 females who had recently undergone aesthetic procedures. These females were concerned about *certain* body areas but found themselves attractive before treatment. There was no general dissatisfaction with the body. All of them had a positive physical self-perception, satisfaction in life, appearance, health, fitness and weight. Most of these females did not search for improved beauty, attractiveness, youthfulness, erotic radiation, happiness in love. Their major motivation was a healthy, natural or happy physical expression, mediating more inner contentment or self-esteem. In all cases it was a rational

not emotional decision for cosmetic procedures. These aesthetical procedures were also perceived as a part of preventive medicine.^{90–92}

The spectrum of procedures is dependent on age. Whereas younger women often seek lip augmentation or correction of asymmetries, volume loss and skin laxity with deeper furrows are major problems of older patients.^{4,5,93,94}

To match patients' expectations, the first step is to identify the nature of complaint. Volume loss and laxity of skin need repeated and often combined approaches to gain good or better results. The final outcome will be dependent filler type and injection, associated medical problems, severity photoaging, smoking and tanning behaviour. Realistic expectations of the patient are a major prerequisite for a successful treatment.

Conclusions

HA dermal filler are safe for treatment of wrinkles and ageing skin when used properly. A qualified dermatologist, ophthalmologist, otolaryngologist or plastic surgeon may use fillers after receiving adequate training in the field. This may be obtained either during postgraduation or at any workshop dedicated to the subject of fillers. The physicians should have a thorough knowledge of the anatomy of the area designated to receive an injection of fillers and the aesthetic principles involved. They should also have a thorough knowledge of the chemical nature of the material of the filler, its longevity, injection techniques, and any possible side effects.^{18,95}

Multisyringe injection of HA filler into the aging face results in a reduction of apparent age from 6.1 to 9 years after 2 to 4 weeks. Full-face correction with HA filler is an important procedure in the armamentarium of anti-aging techniques.⁹⁶ Combining HA filler with other procedures can further improve patient's satisfaction and aesthetic outcome.^{3–5}

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material. Written consent was obtained from the patient or relative for publication of this study.



References

- John HE, Price RD. Perspectives in the selection of hyaluronic acid fillers for facial wrinkles and aging skin. *Patient Prefer Adherence*. 2009;3: 225–30.
- Volpi N, Schiller J, Stern R, Soltés L. Role, metabolism, chemical modifications and applications of hyaluronan. *Curr Med Chem*. 2009;16: 1718–45.
- Wollina U, Goldman A, Berger U, Abdel-Naser MB. Esthetic and cosmetic dermatology. *Dermatol Ther*. 2008;21:118–30.
- Goldman A, Wollina U. Facial rejuvenation for middle-aged women: a combined approach with minimally invasive procedures. *Clin Interv Aging*. 2010;5:293–9.
- Wollina U, Payne CR. Ageing well—the role of minimally invasive aesthetic dermatological procedures in women over 65. *J Cosmet Dermatol*. 2010;9:50–8.
- Kablik J, Monheit GD, LiPing Y, Chang G, Gershkovich J. Comparative physical properties of hyaluronic acid dermal fillers. *Dermatol Surg*. 2009; 35:302–12.
- Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol*. 2007;143:155–63.
- Wesley NO, Dover JS. The filler revolution: a six-year retrospective. *J Drugs Dermatol*. 2009;8:903–7.
- Beer K, Lupo MP. Making the right choices: attaining predictable aesthetic results with dermal fillers. *J Drugs Dermatol*. 2010;9:458–65.
- Gold M. The science and art of hyaluronic acid dermal filler use in esthetic applications. *J Cosmet Dermatol*. 2009;8:301–7.
- Kablik J, Monheit GD, Yu L, Chang G, Gershkovich J. Comparative physical properties of hyaluronic acid dermal fillers. *Dermatol Surg*. 2009;35 Suppl 1: 302–12.
- Gold MH. Use of hyaluronic acid fillers for the treatment of the aging face. *Clin Interv Aging*. 2007;2:369–76.
- Falcone SJ, Berg RA. Temporary polysaccharide dermal fillers: a model for persistence based on physical properties. *Dermatol Surg*. 2009;35: 1238–43.
- Sundaram H, Voigts B, Beer K, Meland M. Comparison of the rheological properties of viscosity and elasticity in two categories of soft tissue fillers: calcium hydroxylapatite and hyaluronic acid. *Dermatol Surg*. 2010; 36 Suppl 3:1859–65.
- Yeom J, Bhang SH, Kim BS, et al. Effect of cross-linking reagents for hyaluronic acid hydrogel dermal fillers on tissue augmentation and regeneration. *Bioconjug Chem*. 2010; 21:240–7.
- Arlette JP, Trotter MJ. Anatomic location of hyaluronic acid filler material injected into nasolabial fold: a histologic study. *Dermatol Surg*. 2008; 34 Suppl 1:S56–62.
- Sclafani AP, Pizzi L, Jutkowitz E, Mueller N, Jung M. FILLERS-Q: an instrument for assessing patient experiences after treatment with facial injectable soft tissue fillers. *Facial Plast Surg*. 2010;26:310–9.
- Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. *Dermatol Surg*. 2008;34:S115–48.
- Ross JJ, Malhotra R. Orbitofacial rejuvenation of temple hollowing with Perlane injectable filler. *Aesthet Surg J*. 2010;30:428–33.
- Liew S, Nguyen DQ. Nonsurgical volumetric upper periorbital rejuvenation: A plastic surgeon's perspective. *Aesthetic Plast Surg*. 2010; in press.
- Morley AM, Malhotra R. Use of hyaluronic acid filler for tear-trough rejuvenation as an alternative to lower eyelid surgery. *Ophthalm Plast Reconstr Surg*. 2010; in press.
- Donath AS, Glasgold RA, Meier J, Glasgold MJ. Quantitative evaluation of volume augmentation in the tear trough with a hyaluronic acid-based filler: a three-dimensional analysis. *Plast Reconstr Surg*. 2010;125:1515–22.
- Morley AM, Taban M, Malhotra R, Goldberg RA. Use of hyaluronic acid gel for upper eyelid filling and contouring. *Ophthalm Plast Reconstr Surg*. 2009;25:440–4.
- Mancini R, Khadavi NM, Goldberg RA. Nonsurgical management of upper eyelid margin asymmetry using hyaluronic acid gel filler. *Ophthalm Plast Reconstr Surg*. 2011;27:1–3.
- Carruthers JD, Carruthers A. Facial sculpting and tissue augmentation. *Dermatol Surg*. 2005;31:1604–12.
- Cattin TA. A single injection technique for midface rejuvenation. *J Cosmet Dermatol*. 2010;9:256–9.
- Fischer TC. A European evaluation of cosmetic treatment of facial volume loss with Juvéderm™ Voluma™ in patients previously treated with Restylane Sub-Q™. *J Cosmet Dermatol*. 2010;9:291–6.
- Hoffmann K; the Juvéderm Voluma Study Investigator Group. Volumizing effects of a smooth, highly cohesive, viscous 20-mg/mL hyaluronic acid volumizing filler: prospective European study. *BMC Dermatol*. 2009;9:9.
- Dayan SH, Arkins JP, Gal TJ. Blinded evaluation of the effects of hyaluronic acid filler injections on first impressions. *Dermatol Surg*. 2010;36 Suppl 3: 1866–73.
- Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Dermatol Surg*. 2008;34 Suppl 1:S2–8.
- Narins RS, Coleman WP 3rd, Donofrio LM, et al. Improvement in nasolabial folds with a hyaluronic acid filler using a cohesive polydensified matrix technology: results from an 18-month open-label extension trial. *Dermatol Surg*. 2010;36 Suppl 3:1800–8.
- Smith SR, Jones D, Thomas JA, Murphy DK, Beddingfield FC 3rd. Duration of wrinkle correction following repeat treatment with Juvéderm hyaluronic acid fillers. *Arch Dermatol Res*. 2010;302:757–62.
- Dirting K, Lampe H, Wolters M, Prager W, Einmüller J. Hyaluronsäure zur Korrektur der Nasolabialfalten—Ergebnisse einer klinischen Studie. *J Dtsch Dermatol Gesellsch*. 2008;6 Suppl 2:S10–4.
- Monheit GD, Baumann LS, Gold MH, et al. Novel hyaluronic acid dermal filler: dermal gel extra physical properties and clinical outcomes. *Dermatol Surg*. 2010;36 Suppl 3:1833–41.
- Humphrey CD, Arkins JP, Dayan SH. Soft tissue fillers in the nose. *Aesthet Surg J*. 2009;29:477–84.
- Klein AW. Soft tissue augmentation 2006: filler fantasy. *Dermatol Ther*. 2006;19:129–33.
- Schweiger ES, Riddle CC, Tonkovic-Capin V, Aires DJ. Successful treatment with injected hyaluronic acid in a patient with lip asymmetry after surgical correction of cleft lip. *Dermatol Surg*. 2008;34:717–9.
- Ogden S, Griffiths TW. A review of minimally invasive cosmetic procedures. *Br J Dermatol*. 2008;159:1036–50.
- Goldman A, Wollina U. Elevation of the corner of the mouth using botulinum toxin type A. *J Cutan Aesth Surg*. 2010;3:145–50.
- De Oliveira Monteiro E. Hyaluronic acid for restoring earlobe volume. *Skinmed*. 2006;5:293–4.
- Becker-Wegerich P. Neue Indikationen für Hyaluronsäure der NASHA™-Gel-Generation—Highlights aus dem ästhetischen dermatologischen Praxisalltag. *J Dtsch Dermatol Ges*. 2008;6 Suppl 3:S3–20.
- Hasson A, Romero WA. Treatment of facial atrophic scars with Esthélic, a hyaluronic acid filler with polydense cohesive matrix (CPM). *J Drugs Dermatol*. 2010;9:1507–1509.
- Skeie L, Bugge H, Negaard A, Bergersen BM. Large particle hyaluronic acid for the treatment of facial lipoatrophy in HIV-positive patients: 3-year follow-up study. *HIV Med*. 2010;11:170–7.
- Bechara FG, Gambichler T, Brockmeyer NH, Sand M, Altmeyer P, Hoffmann K. Hyaluronic acid new formulation: experience in HIV-associated facial lipoatrophy. *Dermatology*. 2008;217:244–249.
- Pavicic T, Ruzicka T, Korting HC, Gauglitz G. Monophasic, cohesive-polydensified-matrix crosslinking-technology-based hyaluronic acid filler for the treatment of facial lipoatrophy in HIV-infected patients. *J Drugs Dermatol*. 2010;9:690–5.
- Elliott L, Rashid RM, Colome M. Hyaluronic acid filler for steroid atrophy. *J Cosmet Dermatol*. 2010;9:253–5.
- Shamban AT. Combination hand rejuvenation procedures. *Aesthet Surg J*. 2009;29:409–13.
- Butterwick KJ. Rejuvenation of the aging hand. *Dermatol Clin*. 2005;23: 515–27.
- Bidic SM, Hafez DA, Rohrich RJ. Dorsal hand anatomy relevant to volumetric rejuvenation. *Plast Reconstr Surg*. 2010;126:163–8.

50. Man J, Rao J, Goldman M. A double-blind, comparative study of nonanimal-stabilized hyaluronic acid versus human collagen for tissue augmentation for the dorsal hands. *Dermatol Surg.* 2008;34:1026–31.
51. Hartmann V, Bachmann F, Plaschke M, Gottermeier T, Nast A, Rzyany B. Handaugmentation mit stabilisierter Hyaluronsäure (Macrolane™ VRF 20 und Restylane® Vital, Restylane® Vital Light). *J Dtsch Dermatol Ges.* 2010;8:41–4.
52. Williams S, Tamburic S, Stensvik H, Weber M. Changes in skin physiology and clinical appearance after microdroplet placement of hyaluronic acid in aging hands. *J Cosmet Dermatol.* 2009;8:216–225.
53. Kwak TI, Oh M, Kim JJ, Moon DG. The effects of penile girth enhancement using injectable hyaluronic acid gel, a filler. *J Sex Med.* 2010: in press.
54. Kwak TI, Jin MH, Kim JJ, Moon DG. Long-term effects of glans penis augmentation using injectable hyaluronic acid gel for premature ejaculation. *Int J Impot Res.* 2008;20:425–8.
55. Carruthers J, Carruthers A, Monheit GD, Davis PG. Multicenter, randomized, parallel-group study of onabotulinumtoxin A and hyaluronic acid dermal fillers (24-mg/mL smooth, cohesive gel) alone and in combination for lower facial rejuvenation: satisfaction and patient-reported outcomes. *Dermatol Surg.* 2010;36 Suppl 4:2135–45.
56. Kenner JR. Hyaluronic acid filler and botulinum neurotoxin delivered simultaneously in the same syringe for effective and convenient combination aesthetic rejuvenation therapy. *J Drugs Dermatol.* 2010;9:1135–8.
57. Goldman MP, Alster TS, Weiss R. A randomized trial to determine the influence of laser therapy, monopolar radiofrequency treatment, and intense pulsed light therapy administered immediately after hyaluronic acid gel implantation. *Dermatol Surg.* 2007;33:535–42.
58. Farkas JP, Richardson JA, Brown S, Hoopman JE, Kenkel JM. Effects of common laser treatments on hyaluronic acid fillers in a porcine model. *Aesthet Surg J.* 2008;28:503–11.
59. Nestor MS, Ablon GR, Stillman MA. The use of a contact cooling device to reduce pain and ecchymosis associated with dermal filler injections. *J Clin Aesthet Dermatol.* 2010;3:29–34.
60. Weinkle SH, Bank DE, Boyd CM, Gold MH, Thomas JA, Murphy DK. A multi-center, double-blind, randomized controlled study of the safety and effectiveness of Juvéderm injectable gel with and without lidocaine. *J Cosmet Dermatol.* 2009;8:205–10.
61. Monheit GD, Campbell RM, Neugent H, et al. Reduced pain with use of proprietary hyaluronic acid with lidocaine for correction of nasolabial folds: a patient-blinded, prospective, randomized controlled trial. *Dermatol Surg.* 2010;36:94–101.
62. Lupo MP, Swetman G, Waller W. The effect of lidocaine when mixed with large gel particle hyaluronic acid filler tolerability and longevity: a six-month trial. *J Drugs Dermatol.* 2010;9:1097–100.
63. Brandt F, Bank D, Cross SL, Weiss R. A lidocaine-containing formulation of large-gel particle hyaluronic acid alleviates pain. *Dermatol Surg.* 2010; 36 Suppl 3:1876–85.
64. Raspaldo H, De Boulle K, Levy PM. Longevity of effects of hyaluronic acid plus lidocaine facial filler. *J Cosmet Dermatol.* 2010;9:11–5.
65. Weinberg MJ, Solish N. Complications of hyaluronic acid fillers. *Facial Plast Surg.* 2009;25:324–8.
66. Cohen JL. Understanding, avoiding, and managing dermal filler complications. *Dermatol Surg.* 2008;34:S92–9.
67. Hirsch RJ, Stier M. Complications of soft tissue augmentation. *J Drugs Dermatol.* 2008;7:841–5.
68. Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomized, comparative, multicenter study. *Dermatol Surg.* 2009;35 Suppl 1:322–30.
69. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. *Dermatol Surg.* 2008;34 Suppl 1:S105–9.
70. Glaich AS, Cohen JL, Goldberg LH. Injection necrosis of the glabella: Protocol for prevention and treatment after use of dermal fillers. *Dermatol Surg.* 2006;32:276–81.
71. Grunebaum LD, Bogdan Allemann I, Dayan S, Mandy S, Baumann L. The risk of alar necrosis associated with dermal filler injection. *Dermatol Surg.* 2009;35 Suppl 2:1635–40.
72. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg.* 2010;3:16–9.
73. Park HJ, Jung KH, Kim SY, Lee JH, Jeong JY, Kim JH. Hyaluronic acid pulmonary embolism: a critical consequence of an illegal cosmetic vaginal procedure. *Thorax.* 2010;65:360–1.
74. Alijotas-Reig J, Miró-Mur F, Planells-Romeu I, Garcia-Aranda N, Garcia-Gimenez V, Vilardell-Tarrés M. Are bacterial growth and/or chemotaxis increased by filler injections? Implications for the pathogenesis and treatment of filler-related granulomas. *Dermatology.* 2010;221:356–64.
75. Rzyany B, Becker-Wegerich P, Bachmann F, Erdmann R, Wollina U. Hyaluronidase in the correction of hyaluronic acid-based fillers: a review and a recommendation for use. *J Cosmet Dermatol.* 2009;8:317–23.
76. Alijotas-Reig J, Hindié M, Kandhaya-Pillai R, Miro-Mur F. Bioengineered hyaluronic acid elicited a nonantigenic T cell activation: implications from cosmetic medicine and surgery to nanomedicine. *J Biomed Mater Res A.* 2010;95:180–90.
77. Van Dyke S, Hays GP, Caglia AE, Caglia M. Severe acute local reactions to a hyaluronic acid-derived dermal filler. *J Clin Aesthet Dermatol.* 2010;3:32–5.
78. Taufig AZ, Szöke A, Kühnel W. Neue Strategie zur Erfassung intradermaler Reaktionen nach Implantation resorbierbarer Dermalfiller. *J Aesthet Chir.* 2009;2:29–6.
79. Massone C, Horn M, Kerl H, Ambros-Rudolph CM, Giovanna Brunasso AM, Cerroni L. Foreign body granuloma due to Matridex injection for cosmetic purposes. *Am J Dermatopathol.* 2009;31:197–9.
80. Huh SY, Cho S, Kim KH, et al. A case of complication after Matridex® injection. *Ann Dermatol.* 2010;22:81–4.
81. Bachmann F, Erdmann R, Hartmann V, Wiest L, Rzyany B. The spectrum of adverse reactions after treatment with injectable fillers in the glabellar region: results from the Injectable Filler Safety Study. *Dermatol Surg.* 2009;35 Suppl 2:1629–34.
82. Descamps V, Landry J, Francès C, Marinho E, Ratzu V, Chosidow O. Facial cosmetic filler injections as possible target for systemic sarcoidosis in patients treated with interferon for chronic hepatitis C: two cases. *Dermatology.* 2008;217:81–4.
83. Grimes PE, Thomas JA, Murphy DK. Safety and effectiveness of hyaluronic acid fillers in skin of color. *J Cosmet Dermatol.* 2009;8:162–8.
84. De Arruda LH, Rocha FT, Rocha A. Studying the satisfaction of patients on the outcome of an aesthetic dermatological filler treatment. *J Cosmet Dermatol.* 2008;7:246–50.
85. Lowe P, Lowe NJ. 3D photography and lip filler: a novel assay. *J Cosmet Laser Ther.* 2007;9:237–40.
86. Gensanne D, Josse G, Schmitt AM, Lagarde JM, Vincensini D. In vivo visualization of hyaluronic acid injection by high spatial resolution T2 parametric magnetic resonance images. *Skin Res Technol.* 2007;13:385–9.
87. Grippaudo FR, Mattei M. High-frequency sonography of temporary and permanent dermal fillers. *Skin Res Technol.* 2010;16:265–9.
88. Hussain R, Schofield M, Loxton D. Cosmetic surgery history and health service use in midlife: Women's Health Australia. *Med J Austr.* 2002;176:576–9.
89. American Society of Plastic Surgeons. Perception of the injection—American women's perception of cosmetic facial injectables. *A Harris Interactive Survey.* December, 2006.
90. Cremers I. Zur gesellschaftlichen Entwicklung des Naturbegriffs in der ästhetischen Dermatologie. *Kosmet Med.* 2004;25:252–9.
91. Cremers I. Aus der Praxis der ästhetisch-plastischen Altersmedizin—Ein Beitrag zur Kulturkritik der Ästhetischen Medizin. *Kosmet Med.* 2010;31:30–6.
92. Cremers I, Wollina U. What is cosmetic dermatology good for? The patients view reflected by a prospective study. *J Eur Acad Dermatol Venereol.* 2005;19 Suppl 2:9.
93. Mandy SH. Satisfying patient expectations with soft-tissue augmentation. *Dermatol Online J.* 2009;15:1.
94. Wollina U, Goldman A. Minimally invasive aesthetic procedures in young adults. *Clin Cosmet Invest Dermatol.* 2011;4: in press.
95. Vedamurthy M; IADVL Dematosurgery Task Force. Standard guidelines for the use of dermal fillers. *Indian J Dermatol Venereol Leprol.* 2008; 74 Suppl:S23–7.
96. Taub AF, Sarnoff D, Gold M, Jacob C. Effect of multisyringe hyaluronic acid facial rejuvenation on perceived age. *Dermatol Surg.* 2010;36:322–8.