

# An update review on recent skin fillers

Li-Ying Cheng<sup>1</sup>, Xiao-Ming Sun<sup>1</sup>, Meng-Yao Tang<sup>1</sup>, Rong Jin<sup>1</sup>, Wen-Guo Cui<sup>2</sup>,  
Yu-Guang Zhang<sup>1</sup>

<sup>1</sup>Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai 200011, China.

<sup>2</sup>Orthopedic Institute, Soochow University, Suzhou 215006, Jiangsu, China.

**Address for correspondence:** Dr. Yu-Guang Zhang, Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, School of Medicine, 639 Zhi Zao Ju Road, Shanghai 200011, China. E-mail: zhangyg18@126.com

## ABSTRACT

Facial rejuvenation has changed over the last decade, evolving from the rhytidectomy to an approach that focuses on revolumization, due to a more complete understanding of the changes to bone and soft tissue that occur with the aging face. Soft tissue augmentation using various injectable filler agents has gained popularity due to their nonsurgical, non-invasive procedures, instant cosmetic outcomes and limited recovery time. The skin filler market is booming and the variety of available skin fillers is increasing, providing the plastic surgeons many choices. Nonpermenant, biodegradable, resorbable agents may induce little complications, but they will normally disappear soon after injection. Semipermanent, biodegradable, biostimulatory, nonresorbable fillers may induce a bit more complications, but they will normally disappear spontaneously in a few months. Permanent, nonresorbable fillers usually give rise to severe complications or reactions which may not disappear spontaneous. They may appear several years after the injection, and treatment is often insufficient. Unfortunately, the ideal filler with lasting effect but without any complication has not been discovered yet. In this review, we give an update on currently available skin filler agents, and what is new in recent 5 years.

## Key words:

Skin fillers; revolumization; biodegradable; biostimulatory; nonresorbable; bovine collagen; hyaluronic acid; polyacrylamide

## INTRODUCTION

The past decade has seen an evolution in the filler market for meaningful volume restoration in the aging face. There are now over 35 major filler product companies worldwide.<sup>[1]</sup> In 2014, there were 2.3 million soft-tissue filler procedures in the United States, an increase of 3% from 2013.<sup>[2]</sup> The days of treating a nasolabial fold with single skin filler injection is gone, and a new era of more sophisticated approach of thoughtful, restrained,

and effective filler injection has come. Deep-volume increase, combinational approaches, natural looking outcomes, and safety measures are the most important considerations for filler use.

Skin fillers on the market today are categorized into transitory biodegradable or resorbable within months and years respectively, and permanent or nonresorbable fillers. Biodegradable agents can be divided into

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** service@oaeublish.com

**How to cite this article:** Cheng LY, Sun XM, Tang MY, Jin R, Cui WG, Zhang YG. An update review on recent skin fillers. *Plast Aesthet Res* 2016;3:92-9.

**Received:** 29-11-2015; **Accepted:** 09-03-2016

### Access this article online

Quick Response Code:



**Website:**  
<http://parjournal.net>

**DOI:**  
10.20517/2347-9264.2015.124.

two categories: (1) nonpermanent fillers, also named replacement fillers (collagen, hyaluronic acid and biological fillers), which has a short duration with typical lengths of several months to one year and are eventually reabsorbed through macrophage activation; (2) semipermanent fillers, or stimulatory fillers (polylactic acid and calcium hydroxylapatite), which have a longer duration of aesthetic improvements lasting up to years with minimal side effects. They will typically result in a foreign body reaction that elicits fibroblast activation and collagenesis at the site of injection. Permanent implants (polymethylmethacrylate, silicone and hydroxyethylmethacrylate) could provide long-lasting revolumization results and could also induce fibrogenesis and collagen production, but with higher potential risk of complications. The skilled hands of the experienced plastic surgeons/dermatologists are required for injection.<sup>[3-5]</sup>

## BIODEGRADABLE FILLERS

Biodegradable fillers are impermanent agents than can last for a limited time of volume augmentation, from months up to 12 months, but will eventually metabolized by the body. Some of the volume effect is due to a transient inflammatory response to skin fillers with associated edema. However, these volume effects will diminish soon after injection.<sup>[6,7]</sup> Subsequent fibroblast activation and neocollagenesis can be another two factors for volume augmentation, but they only result in partial filler engraftment into the surrounding tissue.<sup>[8-10]</sup> Current biodegradable fillers stimulate neocollagenesis for more sustained aesthetic improvements and carry a low risk of adverse events or serious complications. Although permanent agents offer significant clinical benefits, short-term of volume effect, ease of correction and often reversible in the event of adverse effects make biodegradable fillers attractive to patients and plastic surgeons worldwide.

Generally, biodegradable filler spread on the market currently includes: hyaluronic acid (HA), bovine collagen, calcium hydroxylapatite (CaHA) and injectable poly-L-lactic acid (PLLA).

### Bovine collagen

Bovine collagen is a resorbable filler. Bovine collagen was the first facial filler approved by the Food and Drug Administration (FDA) for the correction of contour irregularities in the USA,<sup>[11,12]</sup> which has been used as an injectable filler for almost 30 years. Originally, Bovine collagen was injected into the dermis and subcutaneous tissue to correct viral pockmarks, depressed acne scars, lipoatrophy, deep nasolabial folds, rhytides, and soft tissue augmentation. The duration of the augmentation effect is usually less than 6 months.<sup>[13,14]</sup>

Histopathologically, bovine collagen fibers are much thicker than human collagen, have a homogeneous appearance nearly devoid of spaces between them, with fewer fibroblasts, and fail to refract polarized light. Skin tests are required before the injection of bovine collagen products. Rare hypersensitive reactions, including foreign body

granulomas and palisading granulomas to bovine collagen have been reported. Rare systemic complications include flulike symptoms, paresthesias or difficulty breathing, and severe anaphylactic shock have been reported after injections of bovine collagen.<sup>[15,16]</sup>

The requirement for skin testing before injection to identify patients at risk for allergic reactions and its short duration of effect, particularly in more mobile areas of the face have restricted the popularity of Bovine collagen's usage as a skin filler.<sup>[17]</sup> Although human-based collagen was subsequently developed to lessen the chance of hypersensitivity reaction, the demand for collagen rapidly declined in the face of emerging products that offered long-lasting effects with few side effects.

## Human-derived bioengineered collagen implants

Human-based collagen implants have been developed in recent years, to avoid allergic reactions to bovine collagen. Autologen (Collagenesis, Beverly, MA) is an injectable autologous human tissue matrix primarily composed of intact collagen fibrils that are processed from the patient's own skin and harvested during elective surgery.<sup>[18,19]</sup> Human collagen implants are also obtained from human donor tissues that undergo extensive screening for infectious disease and the material is irradiated before use. The cosmetic effect lasts about 4 to 7 months, depending on the area of treatment, injection technique, and amount of injected collagen.<sup>[17]</sup> No skin test for hypersensitive reactions is required for human-derived collagen products. Local adverse reactions include bruising, erythema, and swelling at the site of injection. Granulomatous reaction at the site of the injection has also been reported in few cases.<sup>[20]</sup>

## HA

Crosslinked animal or non-animal derived HA fillers have been introduced to the market for more than 20 years in the USA and even longer in different countries around the world. Today, HA-based dermal fillers are the fastest non-invasive esthetic procedure in the USA,<sup>[21]</sup> which still remains the most popular dermal filler<sup>[22]</sup> despite the new injectable fillers with different innovative compounds continues to expand.

HA was first discovered by Karl Meyer, who is considered the father of glycosaminoglycan chemistry, and his assistant John Palmer.<sup>[23]</sup> HA is a glycosaminoglycan disaccharide, which exists naturally in the body. Approximately 50% of total HA is found in the skin, and it is produced by dermal fibroblasts, endothelial cells, synovial cells, adventitial cells, smooth muscle cells, and oocytes, and is released into the surrounding extracellular space. The half-life of HA is three days or less.<sup>[4]</sup>

Injections of HA are used for correction the wrinkles of the face, for soft tissue augmentation, and for filling all types of defects. HA has become the most popular skin filler agent, and reached a high patient satisfaction with a low incidence of serious complications. The highly charged nature of HA

provides its high solubility and high water binding affinity, which also contributes to volume augmentation.<sup>[23]</sup> HA may also stimulate neocollagenesis which is another reason for volume augmentation.<sup>[8,24,25]</sup> The injected HA is eventually degraded and cleared by hepatic metabolism as thus the effect diminished.

HA has no organ or species specificity, and therefore in theory there is no risk of an allergic reaction. Very few adverse hypersensitivity reactions secondary to injections of HA used as filler have been reported; in histology, they consisted of a granulomatous foreign body reaction, with abundant multinucleated giant cells surrounding an extracellular basophilic amorphous material, which was the injected hyaluronic acid gel. One favorable character of HA is that it can be easily dissolved with hyaluronidase if there is an undesired or adverse effect. The duration of action averages 6 months with a residual effect lasting up to 2 to 3 years.<sup>[26]</sup> The short longevity is the primary limitation of HA.

Currently available HA dermal fillers, depending on HA concentration, cross-link density, and manufacturing process, has different hydration capacity at equilibrium. Below are some of the favorable HA products by the plastic surgeons and dermatologist.

(1) Restylane® was FDA-approved in December of 2003, which is now the most popular dermal filler. Restylane® has been proven to be safe and effective in the treatment of nasolabial folds in a pivotal multicenter, double-blind clinical study.<sup>[27]</sup> Perlane® is a more viscous version of Restylane®, which was FDA-approved in 2007. Both Restylane® and Perlane® are produced by Q-Med AB in Sweden and distributed in the USA by Medicis Pharmaceutical Corporation. They are based on “nonanimal stabilized hyaluronic acid” and produced from cultures of *Streptococcus equi* via a proprietary process crosslinked with 1,4-butanediol diglycidyl ether giving a final concentration of 20 mg/mL. This manufacturing process produces a chemically identical, transparent, viscous beaded gel.<sup>[28]</sup>

(2) Juvéderm™ Ultra and Juvéderm™ Ultra Plus, FDA-approved in September, 2006, are new injectable HA dermal fillers, which are distributed by Allergan, Inc. The FDA has granted a label extension for Juvéderm™ Ultra and Juvéderm™ Ultra Plus in June, 2007 (Allergan, Inc. 2007). Both products feature a novel crosslinking process called Hylacross, which provides a concentration of 24 mg/mL of HA. Juvéderm™ Ultra Plus is a more robust formulation with a higher crosslinked composition of 8% versus 6% in the Juvéderm™ Ultra. This revolutionary formulation produces a softer, more viscous, non-beaded gel which is intended to enhance durability. The clinical data demonstrates that the effects with a single treatment of Juvéderm™ Ultra or Juvéderm™ Ultra Plus may last for up to 12 months.<sup>[22,29,30]</sup>

(3) Eleveess™ is the latest HA approved by the FDA, in July 2007, which was manufactured by Anika Therapeutics, MA, USA, and was based on chemically modified non-animal HA proprietary technology which incorporates 0.3% lidocaine hydrochloride as a component of the treatment syringe. The concentration of HA in this product is the highest available

at 28 mg/mL.<sup>[22,29,30]</sup>

(4) The HA dermal fillers on the horizon are Puragen, Puragen Plus, Prevelle, Prevelle Plus, Belotero, and Teosyal family of products. Puragen and Puragen plus are based on double crosslinked (DXL™) technology with non-animal HA chains. DXL™ technology increases the resistance to degradation once the product is implanted Hyaluronic acid dermal fillers to come and not yet available in the USA.

Despite its great popularity and satisfying aesthetic outcome, there are some adverse reactions of HA injection. Nonallergic local side effects at the sites of injections are frequent, including pain, bruising, and transient edema, but they disappear in a few days and usually do not need any treatment.<sup>[31]</sup> Too superficial placement of HA fillers or an uneven distribution of the injected product can lead to visible, pale nodules in the skin. Uncommon additional nonallergic reactions include bacterial infections, herpes reactivation, generalized scleromyxedema,<sup>[32]</sup> aseptic abscess,<sup>[33]</sup> scar sarcoidosis,<sup>[34]</sup> and interferon-induced systemic sarcoidosis in patients with chronic hepatitis C, who also developed sarcoidal granulomas around the injected HA filler<sup>[35]</sup> and necrosis and livedoid pattern after accidental arterial embolization.<sup>[36]</sup> Blood vessels-embolism by HA injection is the most severe complications, which may lead to organ necrosis, such as blindness, stroke, which sometimes could be irreversible.

### Platelet-rich plasma

Platelet-rich fibrin matrices (Selphyl System; Aesthetic Factors, LLC, Princeton, N.J.), derived through the collection and centrifugation of blood, is approved by the FDA as a medical device designed for the safe and rapid preparation of autologous platelet-rich plasma (PRP) for use in orthopedic surgery. For cosmetic applications, PRP is injected into the face to stimulate cell proliferation via the release of growth-promoting proteins.<sup>[37]</sup> Histological examination shows activated fibroblasts and new collagen deposition at the site of injection.<sup>[38]</sup> Injection is an office-based procedure used to fill scars and rhytides with only minor transient ecchymosis and edema.<sup>[31,37]</sup> Additional studies are required to evaluate the efficacy and safety of platelet-rich fibrin matrices for soft-tissue augmentation.<sup>[3]</sup>

### PLLA

Injectable PLLA is biocompatible, biodegradable, biostimulatory, synthetic filler that must be injected into the reticular dermis or subcutaneous fat. Polylactic acid as Sculptra® was licensed by FDA in July, 2009.<sup>[39,40]</sup> Sculptra® effects by stimulating neocollagenesis through fibroblast activation,<sup>[41]</sup> thus becomes popular as soft-tissue augmentation filler. Animal studies have revealed that PLLA are able to stimulate the proliferation of dermal fibroblasts with subsequent endogenous production of collagen.<sup>[41,42]</sup> Histological studies in humans have shown gradual dissolution of the injected PLLA and dermal in-growth of type I collagen over 8 to 30 months after injection.<sup>[43,44]</sup> PLLA is gradually degraded by nonenzymatic hydrolysis into water and carbon dioxide over approximately 9 to 24

months.<sup>[45,46]</sup> However, the augmentation effect lasts for at least 24 months due to the neocollagenesis.<sup>[47]</sup>

Short-term adverse events, including swelling, bruising, erythema, pain, inflammation, and pruritus, are frequently, but they usually disappear in a few days. The rate of granuloma formation of Sculptra® has been reported as high as 44%.<sup>[48]</sup> The formation of granuloma greatly influences patient's appearance. Treatment of granulomas includes surgical excision and intralesional injection of corticosteroids.<sup>[49]</sup> Surgical excision is not recommended except as a last resort. The corticosteroids used to treat granulomas need to be injected repeatedly.<sup>[50,51]</sup> There are also severe systemic adverse effects, which is very rare, with only one case reported as an anaphylactic reaction necessitating treatment interruption.<sup>[52]</sup>

## CaHA

CaHA is a biocompatible, biodegradable, resorbable and biostimulatory filler that contains microspheres which can stimulate the endogenous production of collagen. The product has a texture resembling native soft tissue and migration is minimal.<sup>[53]</sup> Histopathologically, microspheres of CaHA stimulate almost no foreign body reaction and they appear bluish in color and round or oval in shape. It is suggested that the microspheres of this implant are degraded by enzymatic breakdown rather than phagocytosis. The microspheres appear packed together, with bluish color, round or oval shape, 25 to 40 µm in size, and surrounded by some fibrin fibers but little cellular infiltrate.

Initial augmentation is afforded by the implant itself, but in a few months the palpable implant diminishes further in size and has disappeared clinically at 9 to 12 months. When macrophages begin to degrade the implant, new collagen may form around the CaHA microspheres.<sup>[54]</sup>

Injectable microspheres of CaHA have been successfully used for correction of lipoatrophy of HIV patients receiving antiprotease treatment and for smoothing moderate wrinkles.<sup>[55-59]</sup> When this agent is injected in the lips, it tends to induce a high incidence of nodules.<sup>[60]</sup> Migration to a distant location from the injection site, a foreign body granulomatous reaction, seen as blue-gray microspheres in the extracellular matrix or within multinucleated giant cells has also been reported.<sup>[61]</sup>

## Polycaprolactone-based dermal filler

A promising new biodegradable collagen stimulatory filler, composed of 70% aqueous carboxymethylcellulose (CMC) gel carrier (Ellans é™, Aqtis Medical, a Sinclair Company; Utrecht, The Netherlands) and 30% synthetic polycaprolactone (PCL) microspheres has recently been introduced to the market. Its unique tuneable longevity gives the dermal filler variable durations for up to 4 years [Ellans é™-S (1 year), Ellans é™-M (2 years), Ellans é™-L (3 years) and Ellans é™-E (4 years)] and is therefore ideal for those seeking long-lasting results.<sup>[62]</sup>

The PCL-based dermal filler is proved to be safe and durable in use in facial treatment and in hand rejuvenation in a clinical trial.<sup>[63,64]</sup> Furthermore, PCL-based dermal filler could

induce neocollagenesis in rabbit tissue.<sup>[65]</sup> In Kim-Jongseo's study, the PCL-based dermal filler was injected intra-dermally in the temporal area in human tissue. The results revealed that PCL-based filler is capable of inducing neocollagenesis for up to 13 months after injected intra-dermally in human tissue. However, further clinically study and safety study should be introduced before it could be finally used as a biostimulatory filler in human.<sup>[62]</sup>

## Cross-linked CMC

Five-eight chemically cross-linked CMC is now available as skin filler for the correction of facial defects and imperfections. It was first used in the pharmaceutical industry since the 1960s as an excipient and for drug delivery. A commercially available product based on cross-linked CMC is Erelle™ (Total Action, Bioitech Italy Ltd, Rome, Italy). It consists of a non-particulate, viscoelastic, monophasic gel based on cross-linked CMC in isotonic saline solution. One study of CMC injection in 350 patients with 3-year follow-up revealed that CMC could effectively and durably correct nasolabial wrinkles for 9-12 months.<sup>[66]</sup> Product reapplication over a 36-month period did not lead to an increase in adverse effects, which always remained rare and of little clinical significance, usually consisting of bruising and redness.<sup>[67]</sup> However, further safety studies and clinical trials should be conducted be finally published in the market.

## Autologous fat

Fat grafting is revolutionizing plastic surgery by providing methodologies to less invasively transfer fatty tissue. The initial attempts at soft-tissue augmentation revolved around the surgical use of autologous fat to reconstruct facial scars in 1893.<sup>[68]</sup> It then were largely used for nasolabial folds injection, forehead augmentation, temporal augmentation, breast augmentation, mid face lift. PRP<sup>[69]</sup> and cell-assisted lipotransfer using adipose-derived stem cells have recent been developed to enhance the survival rate of fat grafting.<sup>[70]</sup> There is certain inconsistent reabsorption rate and longevity lasts once the fat survives.<sup>[71-75]</sup> Adverse effects include prolonged edema and ecchymosis which will fade several days after injection. There is also a risk of necrosis and infection.<sup>[76]</sup> There are also vascular complications, which may lead to vision loss and stroke after injection of fat into the glabella and nasolabial folds have been reported.<sup>[77,78]</sup> Proper injection technique is critical for fat injection.

## PERMANENT FILLERS

Permanent fillers include polymethyl-methacrylate (PMMA), silicone, polyacrylamide hydrogel, polyvinylpyrrolidone-silicone suspension, polyalkylimide gel, polyvinylhydroxide microspheres suspended in polyacrylamide gel and others. Permanent fillers are non-resorbable and could provide long-lasting revolumization results. They could also induce fibrogenesis and collagen production, but complications such as granulomas are more frequent in subcutaneous injection with such filler.<sup>[79]</sup>

## Paraffins

Paraffins were initially used for aesthetic procedures to

restore facial volume and contours, but complications such as granulomas and paraffinomas years after treatment have restricted their use for aesthetic treatment.

## Silicone

No silicone product for soft tissue augmentation has been approved by FDA. The major indication for FDA-approved products is retinal detachment with removal of the material after reattachment. In soft tissue augmentation, removal of silicone is not performed. The use of liquid silicon is off label.<sup>[80]</sup> For decades, horrendous complications have been reported from silicone injections into breasts, and its use has been banned by many authorities. Adverse effects have also been noted after use for facial tissue augmentation.<sup>[81-83]</sup> After illegal silicone injection, the silicone embolism syndrome has been observed with potential fatal outcome in 24% of patients. Symptoms and signs of the “silicone syndrome” include dyspnea, fever, cough, hemoptysis, chest pain, hypoxia, alveolar hemorrhage, and altered consciousness.<sup>[84]</sup> They have almost been abandoned nowadays.

## PMMA

PMMA is rigid, transparent and colorless, thermoplastic permanent skin filler with low cost, easy accessibility, and potential to achieve lasting results. PMMA has been used as an injectable filler to treat hollows and reduce rhytids. PMMA injections have been associated with several side effects; especially they may lead to some undesirable effects in the eyelids and periocular region.

First-generation polymerized PMMA microspheres are purified with diameter greater than 20  $\mu\text{m}$ , which may produce foreign body granulomas; Lemperle *et al.*<sup>[85,86]</sup> postulate that larger PMMA microspheres (30 to 50  $\mu\text{m}$ ) may resist phagocytosis. However, Bachmann *et al.*<sup>[87]</sup> demonstrated that a giant cell reaction still occurs with larger PMMA microspheres. Complications of PMMA injection were classified as nodular masses, inflammation, allergies and skin hypopigmentation. The most affected sides were the lips (46%), followed by periocular, nasolabial folds, forehead, and cheeks. PMMA injection to the periocular region may lead to erythema, hardening of the local tissues, edema, and formation of nodules and eyelid malposition, which are associated with fibrotic nodules, giant cell inflammation. The best treatment for these PMMA injection complications remains uncertain. Corticosteroid injection may have limited efficacy while surgical debulking may achieve favorable results.<sup>[88]</sup>

## Aquamid (polyacrylamide hydrogel)

Aquamid has been used extensively for soft tissue augmentation and body contouring for 2 decades.<sup>[89]</sup> Aquamid is a biocompatible and nonabsorbable hydrogel consisting of 97.5% water and 2.5% cross-linked polyacrylamide (PAAG). The gel is manufactured through polymerization of the acrylamide monomers and N, N'-methylenebisacrylamide.<sup>[89]</sup> Aquamid is currently approved in several countries in Europe, European Conformity marked in Europe in 2001 for facial augmentation and minor body contouring, PAAG is available in more than 40 countries worldwide (Europe,

Asia, the Middle East, and Latin America) and awaiting FDA approval.

After injection, the implant is encapsulated and surrounded by fibroblasts and macrophages, theoretically preventing migration. Many studies have supported the usage of Aquamid for the treatment of various rhytides, facial contouring, and correction of HIV lipoatrophy. PAAG has been evaluated in clinical trials for facial contouring, deep rhytides and folds,<sup>[90-92]</sup> and the correction of facial lipoatrophy<sup>[93,94]</sup> with efficacy similar to nonanimal stabilized hyaluronic acid and duration of at least 1 year when used for the treatment of nasolabial folds.<sup>[95-98]</sup>

For the past decade, Aquamid has gained popularity as injectable filler. Similar to other facial fillers, there have been reported cases of inflammation, nodule and granuloma formation, and delayed hypersensitivity reactions. Histologic analysis of Aquamid injected into the subcutaneous layer revealed bioactive product that underwent cell infiltration and integration into tissues between weeks 1 and 8.<sup>[99]</sup> In some instances, surgical extraction of the polyacrylamide product was necessary to correct the adverse event of nodule formation. Careful attention to injection technique and sterile precautions are necessary to minimize unwanted reactions. In addition, there have been recent recommendations for the usage of prophylactic antibiotics to minimize complications from bacterial injections and biofilm formation when injecting Aquamid.<sup>[100,101]</sup>

## Polyvinylpyrrolidone-silicone suspension

This is a permanent filler comprised of particles of polymerized silicone elastomer, 100-600  $\mu\text{m}$  in size, dispersed in a carrier of polyvinylpyrrolidone (Bioplastique; Uroplasty BV, Geleen, The Netherlands). The suspension has been mostly used for lip augmentation and the correction of facial rhytids. It should be injected in the subcutaneous tissue. They usually remain at the injected site and could avoid from being phagocytosed by macrophages due to the large size of the silicone particles. They would produce a local foreign body reaction and fibrosis, which contributes to the filling effect.<sup>[102]</sup> Local side effects include induration, swelling, and granuloma formation.<sup>[103-105]</sup>

Histopathologically, granulomas secondary to this filler consist of irregularly shaped cystic spaces containing translucent, jagged “popcorn” nonbirefringent particles of varying size dispersed in a sclerotic stroma surrounded by abundant multinucleated foreign body giant cells.<sup>[102-105]</sup>

## Polyalkylimide gel

Polyalkylimide gel is a permanent hydrophilic translucent gel filler composed of a hydrophilic biopolymer with 96% sterile water and 4% polyalkylimide polymer (Bio-Alcamid; Polymekon, Brindisi, Italy), and different from polyacrylamide. It has been used to increase volume in the cheeks in HIV patients with facial lipoatrophy related to antiretroviral therapy and for gluteal augmentation, correction of irregularities after liposculpture, scar depressions, and posttraumatic subcutaneous atrophy and

filling of pectus excavatum or other malformations of the skeleton. Complications secondary to this filler include edema, bruising, nodules, and infections, but no granulomas have been described. Histopathologically, this filler appears as basophilic amorphous material with granular appearance surrounded by sparse numbers of epithelioid histiocytes, foreign body multinucleated giant cells, neutrophils, and red cells.<sup>[106-110]</sup>

## Polyvinylhydroxide microspheres suspended in polyacrylamide gel

This is a permanent filler composed of composed of a suspension of 6 polyvinylhydroxide microspheres suspended in 2.5% polyacrylamide gel (Evolution; ProCytech SA), and has been used mostly for lip augmentation. This is a rarely used filler, and there are not descriptions of adverse reactions to this filler, other than the observation made by Lemperle *et al.*<sup>[49]</sup> who, in their comparative paper on fillers, injected Evolution (and later excised it from the first author's forearm) and found the filler to give little local reaction and diminish slowly over 9 months.<sup>[4]</sup>

## CONCLUSION

Although dermal fillers have been used for decades in aesthetic medicine, the ideal filler is still missing, because all of them known today may cause adverse reactions. Patients' safety is hampered by nonlicensed products and users. These side effects are tend to be less severe after injection with non-permanent or semi-permanent biodegradable skin fillers, which will mostly disappear spontaneously within a few months. Unfortunately, however, after injection with slowly or nonbiodegradable permanent fillers, severe adverse reactions may appear and need active treatment. Follow-up of patients by trained physicians is necessary to reduce risks and initiate early treatment in case of complications. Careful selection of patients and particular selection of products, matching particular needs, and skilled injector is the best way to perform safe three-dimensional rejuvenation and achieve high patient's satisfaction. In the future, individualized, specifically tailored filler with long-lasting effect but with fewer complications might become available.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Pak CS, Lee J, Lee H, Jeong J, Kim EH, Jeong J, Choi H, Kim B, Oh S, Kim I, Heo CY. A phase III, randomized, double-blind, matched-pairs, active-controlled clinical trial and preclinical animal study to compare the durability, efficacy and safety between polynucleotide filler and hyaluronic acid filler in the correction of crow's feet: a new concept of regenerative filler. *J Korean Med Sci* 2014;29 Suppl 3:S201-9.
- 2014 Complete Plastic Surgery Statistic Report. American Society of Plastic Surgeons. Available from: <http://www.plasticsurgery.org/news/plastic-surgery-statistics/2014-plastic-surgery-statistics.html>.
- Carruthers J, Carruthers A, Humphrey S. Introduction to fillers. *Plast Reconstr Surg* 2015;136 Suppl 5:S120-31.
- Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol* 2011;64:1-34.
- Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast Surg* 2005;29:34-48.
- De Boule K. Management of complications after implantation of fillers. *J Cosmet Dermatol* 2004;3:2-15.
- Bertossi D, Sbarbati A, Cerini R, Barillari M, Favero V, Picozzi V, Ruzzenente O, Salvagno G, Guidi GC, Nocini P. Hyaluronic acid: *in vitro* and *in vivo* analysis, biochemical properties and histological and morphological evaluation of injected filler. *Eur J Dermatol* 2013;23:449-55.
- Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. In vivo stimulation of a de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol* 2007;143:155-63.
- Turlier V, Delalleau A, Casas C, Rouquier A, Bianchi P, Alvarez S, Josse G, Briant A, Dahan S, Saint-Martory C, Theunis J, Bensafi-Benaouda A, Degouy A, Schmitt AM, Redoulès D. Association between collagen production and mechanical stretching in dermal extracellular matrix: *in vivo* effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. *J Dermatol Sci* 2013;69:187-94.
- Watson W, Kaye RL, Klein A, Stegman S. Collagen: a clinical overview. *Cutis* 1983;31:543-6.
- Klein AW, Rish DC. Dermatology: bovine injectable collagen. *West J Med* 1985;143:231.
- Knapp TR, Kaplan EN, Daniels JR. Injectable collagen for soft tissue augmentation. *Plast Reconstr Surg* 1977;60:389-405.
- Stegman SJ, Chu S, Bensch K, Armstrong R. A light and electron microscopic evaluation of Zyderm collagen and Zyplast implants in aging human facial skin: a pilot study. *Arch Dermatol* 1987;123:1644-9.
- Douglas RS, Donsoff I, Cook T, Shorr N. Collagen fillers in facial aesthetic surgery. *Facial Plast Surg* 2004;20:117-23.
- Mullins RJ, Richards C, Walker T. Allergic reaction to oral, surgical and topical bovine collagen. Anaphylactic risk for surgeons. *Aust N Z J Ophthalmol* 1996;24:257-60.
- Siegle RJ, McCoy JP, Schade W, Swanson NA. Intradermal implantation of bovine collagen. humoral immune responses associated with clinical reactions. *Arch Dermatol* 1984;120:183-7.
- Sclafani A, Romo T, Jacono AA, McCormick SA, Cocker R, Parker A. Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: clinical observations and histologic findings. *Arch Facial Plast Surg* 2000;2:130-6.
- Fagien S. Facial soft-tissue augmentation with injectable autologous and allogenic human tissue collagen matrix (autologen and dermalogen). *Plast Reconstr Surg* 2000;105:362-73.
- Moody BR, Sengelmann RD. Self-limited adverse reaction to human-derived collagen injectable product. *Dermatol Surg* 2000;26:936-8.
- Wise JB, Greco T. Injectable treatments for the aging face. *Facial Plast Surg* 2006;22:140-6.
- Lupo MP. Hyaluronic acid fillers in facial rejuvenation. *Semin Cutan Med Surg* 2006;25:122-6.
- Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC. Oligosaccharides of hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med* 2002;195:99-111.
- Mansouri Y, Goldenberg G. Update on hyaluronic acid fillers for facial rejuvenation. *Cutis* 2015;96:85-8.
- Turlier V, Delalleau A, Casas C, Rouquier A, Bianchi P, Alvarez S, Josse G, Briant A, Dahan S, Saint-Martory C, Theunis J, Bensafi-Benaouda A, Degouy A, Schmitt AM, Redoulès D. Association between collagen production and mechanical stretching in dermal extracellular matrix: *in vivo* effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. *J Dermatol Sci* 2013;69:187-94.
- Quan T, Wang F, Shao Y, Rittié L, Xia W, Orringer JS, Voorhees JJ, Fisher GJ. Enhancing structural support of the dermal microenvironment activates fibroblasts, endothelial cells, and keratinocytes in aged human skin *in vivo*. *J Invest Dermatol* 2013;133:658-67.
- Duranti F, Salti G, Bovani B, Calandra M, Rosati ML. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 1998;24:1317-25.
- Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 2003;29:588-95.
- Palm MD. Filler frontier: what's new and heading West to the US market. *Semin Cutan Med Surg* 2014;33:157-63.
- Brandt FS, Cazzaniga A. Hyaluronic acid gel fillers in the management of facial

- aging. *Clin Interv Aging* 2008;3:153-9.
30. Mansouri Y, Goldenberg G. Update on hyaluronic acid fillers for facial rejuvenation. *Cuti* 2015;96:85-8.
  31. Pollack SV. Some new injectable dermal filler materials: Hylaform, Restylane and Artecoll. *J Cutan Med Surg* 1999;Suppl 4:S27-35.
  32. Rongioletti F, Cattarini G, Sottofattori E, Reborá A. Granulomatous reaction after intradermal injections of hyaluronic acid gel. *Arch Dermatol* 2003;139:815-6.
  33. Shafir R, Amir A, Gur E. Long-term complications of facial injections with Restylane (injectable hyaluronic acid). *Plast Reconstr Surg* 2000;106:1215-6.
  34. Dal Sacco D, Cozzani E, Parody A, Reborá A. Scar sarcoidosis after hyaluronic acid injection. *Int J Dermatol* 2005;44:411-2.
  35. Descamps V, Landry J, Frances C, Marinho E, Ratzju V, Chosidow O. Facial cosmetic filler injections as possible target for systemic sarcoidosis in patients treated with interferon for chronic hepatitis C: two cases. *Dermatol* 2008;217:81-4.
  36. Schanz S, Schipper W, Ulmer A, Rassner G, Fierlbeck G. Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 2002;146:928-9.
  37. Grossman KL. Hyaluronic acid gel fillers: hypersensitivity reactions. *Aesthet Surg J* 2005;25:403-5.
  38. Leonard JM, Lawrence N, Narin RS. Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. *Dermatol Surg* 2005;31:577-9.
  39. Schierle CF, Casas LA. Nonsurgical rejuvenation of the aging face with injectable poly-L-lactic acid for restoration of soft tissue volume. *Aesthet Surg J* 2011;31:95-109.
  40. Ladewig K, Abberton K, Andrea J O'Connor. Designing *in vivo* bioreactors for soft tissue engineering. *J Biomater Tissue Engineering* 2012;2:1-13.
  41. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. Tissue response and *in vivo* degradation of selected poly-hydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res* 1993;27:1135-48.
  42. Lam SM, Azizadeh B, Graivier M. Injectable poly-L-lactic acid (Sculptra): technical considerations in soft-tissue contouring. *Plast Reconstr Surg* 2006;118:S55-63.
  43. Vleggaar D. Facial volumetric correction with injectable poly-L-lactic acid. *Dermatol Surg* 2005;31:1511-7.
  44. Vleggaar D, Bauer U. Facial enhancement and the European experience with Sculptra (poly-L-lactic acid). *J Drugs Dermatol* 2004;3:542-7.
  45. Athanasiou KA, Niederauer GG, Agrawal CM, Landsman AS. Applications of biodegradable lactides and glycolides in podiatry. *Clin Podiatr Med Surg* 1995;12:475-95.
  46. Spenlehauer G, Vert M, Benoit JP, Boddaert A. *In vitro* and *in vivo* degradation of poly(D, L-lactide/glycolide) acid microspheres made by solvent evaporation method. *Biomater* 1989;10:557-63.
  47. Vleggaar D. Soft-tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg* 2006;118:S46-54.
  48. Valantin MA, Aubron-Olivier C, Ghosn J, Laglenne E, Pauchard M, Schoen H, Bousquet R, Katz P, Costagliola D, Katama C. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study. *AIDS* 2003;17:2471-7.
  49. Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. *Plast Reconstr Surg* 2006;118:S92-107.
  50. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. *Semin Arthritis Rheum* 2013;43:241-58.
  51. Fan M, Liao J, Guo G, Ding Q, Yang Y, Luo F, Qian Z. Dexamethasone-loaded poly (D,L-lactic acid) microspheres/poly (ethylene glycol) = poly (epsilon-caprolactone) – poly (ethylene glycol) micelles composite for skin augmentation. *J Biomed Nanotechnol* 2014;10:592-602.
  52. Lafaurie M, Dolivo M, Porcher R, Rudant J, Madelaine I, Molina JM. Treatment of facial lipoatrophy with intradermal injections of polylactic acid in HIV-infected patients. *J Acquir Immune Defic Syndr* 2005;38:393-8.
  53. Tzikas TL. Evaluation of the radiance FN soft tissue filler for facial soft tissue augmentation. *Arch Facial Plast Surg* 2004;6:234-9.
  54. Marmur ES, Phelps R, Goldberg DJ. Clinical, histologic and electron microscopic findings after injection of a calcium hydroxylapatite filler. *J Cosmet Laser Ther* 2004;6:223-6.
  55. Broder KW, Cohen SR. An overview of permanent and semipermanent fillers. *Plast Reconstr Surg* 2006;118:75-145.
  56. Silvers SL, Eviatar JA, Echavez MI, Pappas AL. Prospective, open-label, 18-month trial of calcium hydroxylapatite (Rad-iesse) for facial soft-tissue augmentation in patient with human immunodeficiency virus-associated lipoatrophy: one-year durability. *Plast Reconstr Surg* 2006;118:S34-45.
  57. Sklar JA, White SM. Radiance FN: a new soft tissue filler. *Dermatol Surg* 2004;30:764-8.
  58. Jansen DA, Graivier MH. Evaluation of calcium hydroxylapatite based implant (Radiessé) for facial soft-tissue augmentation. *Plast Reconstr Surg* 2006;118:S22-30.
  59. Ahn MS. Calcium hydroxylapatite: Radiessé. *Facial Plast Surg Clin North Am* 2007;15:85-90.
  60. Duffy DM. Complications of fillers. Overview. *Dermatol Surg* 2005;31:1626-33.
  61. Beer KR. Radiessé nodule of the lips from a distant injection site: report of a case and consideration of etiology and management. *J Drugs Dermatol* 2007;6:846-7.
  62. Kim JA, Van Abel D. Neocollagenesis in human tissue injected with a polycaprolactone-based dermal filler. *J Cosmet Laser Ther* 2015;17:99-101.
  63. Moers-Carpi MM, Sherwood S. Polycaprolactone for the correction of nasolabial folds: a 24-month, prospective, randomized, controlled clinical trial. *Dermatol Surg* 2013;39:457-63.
  64. Figueiredo VM. A five-patient prospective pilot study of a polycaprolactone based dermal filler for hand rejuvenation. *J Cosmet Dermatol* 2013;12:73-7.
  65. Nicolau PJ, Marijnissen-Hofsté J. Neocollagenesis after injection of a polycaprolactone based derma filler in a rabbit. *Eur J Aesthet Med Dermatol* 2013;3:19-26.
  66. Leonardis M, Palange A. New-generation filler based on cross-linked carboxymethylcellulose: study of 350 patients with 3-year follow-up. *Clin Interv Aging* 2015;10:147-55.
  67. Leonardis M, Palange A, Dornelles RF, Hund F. Use of cross-linked carboxymethyl cellulose for soft-tissue augmentation: preliminary clinical studies. *Clin Interv Aging* 2010;5:317-22.
  68. Neuber F. Fettransplantation. *Chir Kongr Verhandl Dtsch Gesellch Chir* 1893;22:66.
  69. Cervelli V, Palla L, Pascali M, De Angelis B, Curcio BC, Gentile P. Autologous platelet-rich plasma mixed with purified fat graft in aesthetic plastic surgery. *Aesthetic Plast Surg* 2009;33:716-21.
  70. Sterodimas A, De Faria J, Nicaretta B, Papadopoulos O, Papalambros E, Illouz YG. Cell-assisted lipotransfer. *Aesthet Surg J* 2010;30:78-81.
  71. Ersek RA. Transplantation of purified autologous fat: a 3-year follow-up is disappointing. *Plast Reconstr Surg* 1991;87:219-27.
  72. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. *Aesthetic Plast Surg* 1995;19:421-5.
  73. Fulton JE, Suarez M, Silverton K, Barnes T. Small volume fat transfer. *Dermatol Surg* 1998;24:857-65.
  74. Fournier PF. Fat grafting: my technique. *Dermatol Surg* 2000;26:1117-28.
  75. Kanchwala SK, Bucky LP. Facial fat grafting: the search for predictable results. *Facial Plast Surg* 2003;19:137-46.
  76. Cheng JT, Perkins SW, Hamilton MM. Collagen and injectable fillers. *Otolaryngol Clin North Am* 2002;35:73-85.
  77. Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg* 2014;134:1197-201.
  78. Hong DK, Seo YJ, Lee JH, Im M. Sudden visual loss and multiple cerebral infarction after autologous fat injection into the glabella. *Dermatol Surg* 2014;40:485-7.
  79. Yamauchi PS. Emerging permanent filler technologies: focus on aquamid. *Clin Cosmet Investig Dermatol* 2014;7:261-6.
  80. Peters W, Fornasier V. Complications from injectable materials used for breast augmentation. *Can J Plast Surg* 2009;17:89-96.
  81. Altmeyer MD, Anderson LL, Wang AR. Silicone migration and granuloma formation. *J Cosmet Dermatol* 2009;8:92-7.
  82. Schwartzfarb EM, Hametti JM, Romanelli P, Ricotti C. Foreign body granuloma formation secondary to silicone injection. *Dermatol Online J* 2008;14:20.
  83. Ficarra G, Mosqueda-Taylor A, Carlos R. Silicone granuloma of the facial tissues: a report of seven cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94:65-73.
  84. Schmid A, Tzur A, Leshko L, Krieger BP. Silicone embolism syndrome: a case report, review of the literature, and comparison with fat embolism syndrome. *Chest* 2005;127:2276-81.
  85. Vent J, Lemperle G. Prevention and treatment of complications after polymethylmethacrylate-microspheres injections. *Facial Plast Surg* 2014;30:628-34.
  86. Lemperle G, Nacul AM, Fortes FB. Can injection of PMMA-microspheres cause hypercalcemia? *Clin Cases Miner Bone Metab* 2015;12:82-3.
  87. Bachmann F, Erdmann R, Hartmann V, Becker-Wegerich P, Wiest L, Rzyany B. Adverse reactions caused by consecutive injections of different fillers in the same facial region: risk assessment based on the results from the injectable filler safety study. *J Eur Acad Dermatol Venereol* 2011;25:902-12.
  88. Limongi RM, Tao J, Borba A, Pereira F, Pimentel AR, Akaiishi P, Velasco E Cruz AA. Complications and management of polymethylmethacrylate (PMMA) injections to the midface. *Aesthet Surg J* 2016;36:132-5.

89. Christensen LH, Breiting VB, Aasted A, Jørgensen A, Kebuladze I. Long-term effects of polyacrylamide hydrogel on human breast tissue. *Plast Reconstr Surg* 2003;111:1883-90.
90. Breiting V, Aasted A, Jørgensen A, Opitz P, Rosetzky A. A study on patients treated with polyacrylamide hydrogel injection for facial corrections. *Aesthetic Plast Surg* 2004;28:45-53.
91. Von Buelow S, Von Heimburg D, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation. *Plast Reconstr Surg* 2005;116:1137-46.
92. Von Buelow S, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation in a 2-year follow-up: a prospective multicenter study for evaluation of safety and aesthetic results in 101 patients. *Plast Reconstr Surg* 2006;118:S85-91.
93. De Santis G, Jacob V, Baccarani A, Pedone A, Pinelli M, Spaggiari A, Guaraldi G. Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: a 2-year clinical experience. *Plast Reconstr Surg* 2008;121:644-53.
94. Negredo E, Puig J, Aldea D, Medina M, Estany C, Pérez-Alvarez N, Rodríguez-Fumaz C, Muñoz-Moreno JA, Higuera C, Gonzalez-Mestre V, Clotet B. Four-year safety with polyacrylamide hydrogel to correct antiretroviral-related facial lipoatrophy. *AIDS Res Hum Retroviruses* 2009;25:451-5.
95. Wolters M, Lampe H. Prospective multicenter study for evaluation of safety, efficacy, and esthetic results of crosslinked polyacrylamide hydrogel in 81 patients. *Dermatol Surg* 2009;35 Suppl 1:338-43.
96. Mole B, Gillaizeau F, Carbonnel E, Pierre I, Brazille P, Grataloup C, Mercier S, Duracinsky M, Weiss L, Piketty C. Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: results of the LIPOPHILL open-label study. *AIDS Res Hum Retroviruses* 2012;28:251-8.
97. Lafaurie M, Dolivo M, Girard PM, May T, Bouchaud O, Carbonnel E, Madelaine I, Loze B, Porcher R, Molina JM; ANRS 132 SMILE study group. Poly lactic acid vs. polyacrylamide hydrogel for treatment of facial lipoatrophy: a randomized controlled trial [Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) 132 SMILE]. *HIV Med* 2013;14:410-20.
98. Narins RS, Coleman WP 3rd, Rohrich R, Monheit G, Glogau R, Brandt F, Bruce S, Colen L, Dayan S, Jackson I, Maas C, Rivkin A, Sclafani A, Spivak JC. 12-Month controlled study in the United States of the safety and efficacy of a permanent 2.5% polyacrylamide hydrogel soft-tissue filler. *Dermatol Surg* 2010;36 Suppl 3:1819-29.
99. Fernández-Cossío S, Castaño-Oreja MT. Biocompatibility of two novel dermal fillers: histological evaluation of implants of a hyaluronic acid filler and a polyacrylamide filler. *Plast Reconstr Surg* 2006;117:1789-96.
100. Christensen L, Breiting V, Bjarnsholt T, Eickhardt S, Høgdall E, Janssen M, Pallua N, Zaat SA. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. *Clin Infect Dis* 2013;56:1438-44.
101. Nygart JF, Nygart VA, Borggren M, Tvede M. Effect of prophylactic antibiotics on polyacrylamide gel safety in facial augmentation. *J Drugs Dermatol* 2014;13:571-3.
102. Ersek RA, Beisang AA 3rd. Bioplastique: a new texture copolymer microparticle promises permanence in soft tissue augmentation. *Plast Reconstr Surg* 1991;33:693-702.
103. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Bioplastiquegranulom. *Hautarzt* 1997;48:749-52.
104. Hoffmann C, Schuller-Petrovic S, Soyer HP, Kerl H. Adverse reactions after cosmetic augmentation with permanent biologically inert implant materials. *J Am Acad Dermatol* 1999;40:100-2.
105. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol* 1999;23:113-7.
106. Margolis DM. Treatment for lipoatrophy: facing the real costs. *AIDS* 2007;21:1819-20.
107. Nelson L, Stewart KJ. Experience in the treatment of HIV-associated lipodystrophy. *J Plast Reconstr Aesthet Surg* 2008;61:366-71.
108. Karim RB, De Lint CA, Van Galen SR, Van Rozelaar L, Nieuwkerk PT, Askarizadeh E, Hage JJ. Long-term effect of polyalkylimide gel injections on severity of facial lipoatrophy and quality of life of HIV-positive patients. *Aesthetic Plast Surg* 2008;32:873-8.
109. Mallewa JE, Wilkins E, Vilar J, Mallewa M, Doran D, Back D, Pirmohamed M. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. *J Antimicrob Chemother* 2008;62:648-60.
110. Hönig J. Cheek augmentation with Bio-Alcamid in facial lipoatrophy in HIV seropositive patients. *J Craniofac Surg* 2008;19:1085-8.