Dermal fillers for tissue augmentation: an overview

Injizierbare Füllmaterialien zur Gewebeaugmentation: eine Übersicht

Abstract

Treatments with dermal fillers for tissue augmentation constitute the majority of all non-surgical procedures in plastic surgery. Newly developed products get launched and the market grows continuously, but the “ideal” substance has yet not been found. The substances used these days are high molecular compounds. They have substantial differences in their physicochemical properties and are suspended in complex matrices. This overview describes the latest history of dermal fillers and the commonly used substances of different origin and formalizes the need for the development of systematic procedures of standardized pre-clinical tests with subsequent certification as well as the establishment of interdisciplinary clinical guidelines to ensure customer’s safety.

Introduction

With over 2 million treatments per year, dermal fillers for tissue augmentation make up a quarter of all non-surgical procedures in plastic surgery [1]. They may be used to correct single deep furrows, multiple fine lines or depressed scars. Filling materials are applied by injecting them underneath and within tissue areas using thin cannulas to create a smoother, firmer appearance and to replace volume loss. Depending on the type of filler material being used, they are expected to last several months or even years. Suitable injection sites are the nasolabial fold, perioral and mento-labial folds and the glabella fold. Newly developed products get launched and the market of synthetic substances and various compositions grows continuously. This shows that the “ideal” substance has yet not been found. The substances used these days are high molecular compounds. They have substantial differences in their physicochemical properties and are suspended in a complex matrix. They can be categorized into two groups – absorbable and non-absorbable materials, differing from each other in origin and production (Table 1).

Dermal fillers based on collagen

Collagens are fibrous extra-cellular proteins and make up the main component of soft tissue. Fillers based on collagen are used mainly for facial wrinkle reduction and for the enhancement of facial contour. At first, fillers based on collagen were made of bovine collagen (e.g. Zyderm®, Zyplast®). The high standard of manufacturing procedures combined with the isolation of animals practically excluded the risk of a contamination with BSE. Allergies towards bovine collagen made hypersensitivity testing prior treatment a requirement. With time, this lead to the gradual replacement of bovine collagen by the launch of human and porcine collagen products. The
treatment with autologous human collagen (e.g. Autologen®) is a two-step process. At first, skin tissue is obtained surgically from a patient. Following that, collagen (mainly type I) gets extracted, sterilized and transferred into an injectable collagen suspension. This takes 3 to 4 weeks [2]. Allogenic human collagen is either obtained from skin fibroblast cultures (Cosmoderm®, Cosmoplast®) or micro-particles of decellularized dermis (Cymetra®). Autologous and allogenic human collagens are not the only substances that do not require pre-treatment skin testing; fillers based on collagen derived from porcine skin (Evolence®) have an equally high biocompatibility. In 1985, an alternative to the pre-existing collagens was developed which is particularly interesting for treating scars. Autologous-xenogeic gelatine matrix (Fibrel®) combines porcine collagen with patient blood. Preceding allergy testing is necessary but successful outcomes last 3–12 months [3].

Dermal fillers based on the glycosaminoglycan hyaluronic acid

Hyaluronic acid [(C_{14}H_{21}NO_{11})_n], a glycosaminoglycan, is one of the main components of the extracellular matrix of the dermis in addition to other proteoglycans. It may be used without previous hypersensitivity testing. Hyaluronic acid has hydrophilic properties, therefore it can stabilize the connective tissue by binding water molecules at the injection site. They are a popular choice for enhancing facial contour, enlargement of certain areas of the body, reducing wrinkles by filling in lines as well as correcting imperfections of the face. The substance was originally derived from chemically modified avian hyaluronic acid (e.g. Hylaform®). Nowadays it is genetically engineered using bacterial fermentation (e.g. Streptococcus equi). The products differ from each other in the way the hyaluronic acid molecules are cross-linked with each other. Un-cross-linked hyaluronic acid is composed of molecules in their natural length. By adding cross-linking agents (e.g. Butandioldiglycidylether/BDDE) it is possible to elongate the natural chain of molecules, creating a meshwork and cross-links between the hyaluronic acid molecules. On top of that, cross-linking also stabilizes the molecules and delays their breakdown, prolonging the water binding properties. Biphasic products are mixtures of cross-linked and non-cross-linked hyaluronic acids, (e.g. Restylane®). Their more viscous consistency leads to a greater and longer lasting volume restoration. Monophasic products are products made of either cross-
linked or non-cross-linked hyaluronic acids (e.g. Belotero®, Juvederm®) and are supposed to be softer and able to spread more evenly within the tissue. However, since monophasic products induce a less effective tissue reaction compared to biphasic ones, they come along with a less extensive plumping up effect [4], [5], [6], [7]. By raising the amount of cross-links and increasing homogeneity it is possible to create 3D-matrices, which are able to correct even deeper creases and lipatrophies. Xenogenous-alloplastic combinations combine hyaluronic acid with dextran microparticles (e.g. Reviderm intra®) or undissolved amino-acids (e.g. Jalupro®). They were designed to either induce the formation of new connective tissue after the degradation of the hyaluronic acid or to stimulate reepithelialisation of the skin. However, due to lack of knowledge about possible long-term side effects the societies of plastic surgeons and dermatologists discourage the use of such products [8].

**Synthetic fillers**

Filling materials of neither bacterial nor animal origin are usually based on compositions that contain poly-L-lactic acid, polyvinyl alcohol or hydroxylapatite. Crystalline poly-L-lactic acid is used in the form of lyophilisating implants made of polylactate-microparticles, mannitol and carboxymethyl cellulose (e.g. Sculptra®). Treatments offer degradation at a controllable rate as well as having a stimulating effect on collagen synthesis. According to clinical studies, the results may last up to 18 months if the dermal filler is applied gradually over 2–3 treatments scheduled 4–6 weeks apart [9]. Polyvinyl alcohol [CnH2nO] is a synthetic thermoplastic polymer filling material in the form of a hydrogel that is supposed to create a long lasting temporary effect of up to 1.5 years (Bioinblue®). Small-particle calcium hydroxyapatite [Ca₉(OH)(PO₄)₄] suspended in carboxymethyl cellulose as a gel carrier (e.g. Radiesse®) are supposed to show good effects on deep naso-labial crease and on marionette lines on the chin due to their long-lasting stimulating effect on collagen synthesis [10], [11]. Moreover, they are used in particular for HIV-associated lipoatrophy [12], [13].

**Permanent fillers**

Permanent fillers are synthetic materials, synthetic-collagen-mixtures or synthetic-hyaluronic acid mixtures. They create a permanent augmentation effect by a homogenous tissue reaction. The most commonly used substance is polyacrylamide, the product of a polymerisation reaction of acrylamide and N,N-Methylylisacrylamidmonomeress. Suspended in an aqueous gel, polyacrylamide (e.g. Aquamid®, Bio-Alcamid®, Outline®) has a long half-life and is used mainly for augmentation of the nasolabial fold and the glabellar fold, the corners of the mouth and for the correction of facial defects on cheeks, chin and nose. Most of the permanent xenogenous-alloplastic combina-

**Conclusion**

Experience has shown that the large number of both potential (e.g. aesthetic) and necessary (e.g. reconstructive) treatments and the vast range of applications cannot be covered by a single ideal filling material. It will remain inevitable that with every patient the indication together with the advantages and disadvantages of the treatment need to be carefully evaluated before deciding on a filler material. Although permanent fillers have been used for decades, the long term effects and consequences of biological degradation are mostly unknown. As a result of clinical experience and retrospective studies they are more carefully watched these days. To ensure costumer safety beyond a level of well-founded research, it would be desirable to develop systematic procedures of standarized pre-clinical tests with subsequent certification. The establishment of interdisciplinary clinical guidelines in combination with a central database for documentation of results and side effects with an additional introduction of a patient card would further increase customer safety.

**Notes**

**Competing interests**

The authors declare that they have no competing interests.
References


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