

## Normal and Pathologic Tissue Reactions to Soft Tissue Gel Fillers

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### SUMMARY

- A clinical review based on 6½ years experience from experimental/clinical studies and biopsies from unreactive normal tissues and tissues from adverse reactions.
- The review explains how host tissue reacts to different gel types and how adverse events differed pending on the gel types used.
- Gel fillers for soft tissue augmentation can be divided into two: homogenous, polymer gels and combination gels.
- Adverse events include bacterial infection for the hydrophilic polymer gel and fibrous granulomas for all the other gel types.
- If an infection is initially treated with steroids, Non-Steroid Anti-Inflammatory Drugs (NSAIDs), a weak or a broad-spectrum antibiotic in low dosage, the infection may be aggravated with monstrous swelling, and late symptoms including localized redness, pain, fistulation and purulent secretion may ensue.
- Infectious nodules must be treated with appropriate antibiotics. Granulomas must be treated with a combination of steroids and antibiotics or excision.

## BACKGROUND and INTRODUCTION

- Gel fillers for soft tissue augmentation comprise a wide range of products, which differ in composition and tissue interaction as well as in the type of delayed reaction, they may evoke.
- Two principally different gel types exist: homogeneous, polymer gels and combination gels.
- All gels act as foreign bodies and elicit a foreign body response from the host tissue. This response ranges from a few macrophages that disappear again to an intense foreign-body reaction with fibrosis, all depending on gel type. For polymer gels the filling effect stems from their volume. For combination gels it stems from the intended foreign body reaction to the micro-particles.
- The study is based on observations during 6½ years from experimental/clinical studies and biopsies from adverse reactions as well as from normal unreactive tissues.

### Study objective

The purpose of the review is to explain how host tissue reacts with different gel types and how adverse reactions differ depending on gel type.

### Homogeneous gels

Homogenous or polymer gels are by far the most commonly used soft tissue fillers, comprising both non-degradable and degradable types. Homogenous gels are also called volumetric gels, because the filling effect stems from the gel itself.

#### Degradable gels

The degradable hydrophilic polymer gels have a close resemblance to substances normally present in the tissue. These gels are all degraded by naturally occurring enzymes, but the process can be delayed by adding chemical cross-bindings to the product. This has been done to the hyaluronic acid gel, making the substance very different from the naturally occurring one.

#### Non-degradable gels

The only two non-degradable polymer gels are the hydrogel gels (polyacrylamide) and the silicone gel. The polyacrylamide gel is hydrophilic and consists of a backbone of polyacrylamide to which water molecules are attached. These molecules are readily exchanged with those of the surrounding host tissue. Over time macrophages enter the gel and are gradually replaced by a scaffold of thin connective tissue fibers.

The silicone hydrophobic gel is dispensed in the tissue as rounded vacuoles or droplets, which do not interact with the host tissue. The gel is immobile and prone to molecular condensation. Migration to the reticuloendothelial system by circulating macrophages and foreign-body giant cells has been described.

#### Late adverse reactions

The hydrogel is in a state of constant undulation, because of its continuous water exchange with the host tissue. This results in a minimal fibrous response for both polyacrylamide and hyaluronic acid gels. Late adverse reactions specific for these gels are bacterial infections, which become clinically symptomatic 8-12 days after the injection. Considerable confusion as to the nature of these infections exists, because cultures aimed at identifying pathogenic bacteria are usually negative. The microscopic appearance of all these lesions, however, is the same: gel surrounded by numerous enlarged macrophages and foreign-body giant cells, mixed with polymorphonuclear granulocytes and sometimes identifiable bacteria.

For the degradable gels, adverse reactions are often described as granulomatous allergic tissue reactions developing into abscesses, localized granulomatous reactions, sterile abscesses, foreign-body nodules, or delayed hypersensitivity reactions. The infection may disappear spontaneously along with the degradation of the gel.

Silicone gel is the only polymer gel that gives rise to a so-called granuloma, defined as a firm nodule which consists of

fibrotic tissue and chronic inflammatory cells surrounding droplets or vacuoles of the foreign material. Because of its inability to interact with host tissue the silicone gel may be more prone to harbour a static biofilm than the hydrophilic gels. If bacteria are introduced, they may give rise to a low-grade chronic infection with ensuing fibrosis - a granuloma.

### **Treatment of late adverse reactions**

With non-degradable gels the infection must be treated with a broad-spectrum antibiotic in high dosage. Previous and ongoing studies have shown that the majority of contaminating bacteria belong to the so-called nonpathogenic species and therefore cause a low-grade infection. Only if treated with steroids, non-steroid anti-inflammatory drugs (NSAIDs), a weak antibiotic, or a broad-spectrum antibiotic in low dosage, the infection may become severe with monstrous swelling, and late symptoms including localized redness, pain, fistulation, and purulent secretion may ensue.

Also reinfection has been seen, if the gel was injected too superficially to the surface. In such cases the infection has been resolved by gel removal followed by a course of antibiotics.

## **Combination gels**

Combination gels or structural gels form a large group of two-component fillers consisting of solid microparticles dissolved in a carrier gel. Some particles are non-degradable; others are slowly degraded within 3-5 years. The microparticles remain in the tissue after the carrier gel has disappeared and elicit an intended foreign-body reaction, which results in fibrosis. For degradable gels the fibrous scar tissue is solely responsible for the filling effect. For non-degradable gels the solid microparticles add to the filling effect.

### **Late adverse reactions**

Granulomas with fibrosis may appear after injection of combination gels. Microscopically, microparticles, or partially degraded remnants of them lie embedded in the fibrous tissue, which also contains chronic inflammatory cells, areas of necrosis and a moderate amount of macrophages and foreign-body giant cells.

### **Treatment of late adverse reactions**

Several different treatments including steroids, 5-fluorouracil, alluropurinol, and antibiotics have been suggested, in some cases with resolution of the granulomas. The current most effective treatment has proven to be intralesional injections of a combination of steroids and antibiotics, but many granulomas end up being removed surgically.

## **CONCLUSION**

Dermal gels differ in tissue interaction depending on their nature and composition.

The polymer gels are volumetric, and the filling effect stems from the gel itself. Combination gels are structural, because the filling effect stems from the foreign-body response provoked by the microparticles. All fillers, degradable and non-degradable, can give rise to occasional 'inflammatory nodules' or 'granulomas'.

For hydrophilic gels, infection from bacterial contamination during injection is the cause of the so-called inflammatory nodules.

For the hydrophobic gel, silicone, real foreign-body granulomas have been observed up to many years after the injection. It is suspected that the mechanism behind this late complication is due to a low-grade chronic infection taking place in a biofilm, which have the opportunity to settle at any time after bacteria have been introduced, because the silicone droplets are immobile and not interacting with the surrounding tissue.

A similar biofilm-assisted low-grade infection is suspected to be behind the granulomas occurring after the injection of the combination gels. These 'real' foreign-body granulomas may develop as long as the silicone droplets or the microparticles of the combination gels remain.



## CONTURA

Contura is a medical technology company based in Denmark that develops and commercializes soft tissue fillers.

Contura's products – Aquamid® for facial contouring and Bulkamid® for the treatment of female urinary incontinence – are manufactured using the company's patented polyacrylamide hydrogel technology.

Aquamid is sold through a network of local distributors in 40 countries. Ethicon Inc., a Johnson & Johnson company, holds the exclusive worldwide distribution rights for Bulkamid, which is available in Europe.

Clinical trials evaluating Aquamid and Bulkamid are ongoing in the United States. Data from these trials will be used to support FDA applications for these products. Aquamid and Bulkamid are not approved for sale in the US.

Contura's products are developed, manufactured and tested in Denmark in compliance with the European regulatory requirements for medical devices.

## AQUAMID

Aquamid® is a soft volume filler, which integrates with the body's own tissue and gives a natural look and feel. Produced using Contura's patented hydrogel technology, Aquamid is composed of app. 97.5% non-pyrogenic water and 2.5% cross-linked polyacrylamide and enjoys an unmatched track record of continuous high levels of patient satisfaction.

Aquamid was approved in Europe in 2001 and is available in 40 countries worldwide. Over 350,000 Aquamid injections have been performed to date.

Science has always been the driving force behind Aquamid products. The efficacy and safety of Aquamid have been documented in more than a dozen clinical trials involving more than 5,000 patients. These studies have been published in peer-reviewed journals.

It is currently under clinical investigation in the U.S. for the aesthetic treatment of nasolabial folds. For more information please visit [www.aquamid.com](http://www.aquamid.com).