

# Bioengineered dermal substitutes for periocular defects

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**Abstract:** Bioengineered materials are used as a substitute in many fields of medicine, especially in plastic surgery and in burns. In ophthalmic plastic surgery they can be used for covering large tissue defects or as a tarsal plate substitute, in cases when it is not possible to use conventional surgical techniques. We have searched PubMed and Web of Science scientific databases. We can generally categorize skin substitutes by the type of tissue used—we distinguish autografts, allografts, and xenografts. There are also completely synthetic substitutes. The aim of our article was to summarize the current state of knowledge and to sum up all the clinical applications of bioengineered materials in the periocular region. There are only a few scientific articles about this topic and lack of prospective randomized studies aimed on use of bioengineered materials in periocular region. Nevertheless, there are many articles describing successful case reports or case reports series. According to literature, bioengineered materials are the most commonly used in big traumas or large surgical defects, especially in oculoplastic tumour surgery. Bioengineered dermal substitutes are not frequently used in the periocular region. Dermal substitutes are useful, when it is not possible to close the defect with any other conventional surgical technique.

**Keywords:** Periocular surgery; bioengineered material; oculoplastic surgery; autograft; allograft; xenograft

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## Introduction

Large skin defects of the periocular region can be traditionally reconstructed using regional flaps or free grafts (1). For good cosmetic and functional results, it is necessary to make primary reconstruction of the defect, even though small-size defects can be left to be healed secondarily. Sometimes, there are patients in whom it is not possible to use grafting or flaps—for example in patients with tight facial skin, patients after multiple surgeries in the region or patients with severe tissue loss, either following trauma, especially burns, or elective surgery. In such cases,

a proper alternative of the traditional approach can be using bioengineered dermal substitutes. The aim of our work is to review the literature about using dermal substitutes in the clinical practice.

We can generally categorize skin substitutes by the type of tissue used—we distinguish autografts, allografts, and xenografts (2). There are also completely synthetic substitutes. It is also important whether the substitute replaces dermis or epidermis, this will be discussed in following parts of the article (3,4). In the following part of the article, we will discuss all these subtypes from the general and from the oculoplastic point of view.

## Autografts

All ophthalmic plastic surgeons are familiar with autografts that can be obtained from various anatomical regions from the patients themselves (1). In this part, we would like to aim on the cultured autografts, not on grafts obtained in the standard fashion. In principle, a small tissue sample obtained during biopsy can provide the patient's own keratinocytes or other parts of the skin for culture. There are several commercially available products.

- ❖ Epicel (sometimes called cultured epidermal autograft, or CEA) are cultured keratinocytes grown into sheets of skin. It is traditionally used in the management of severe burns or chronic lower extremity ulcers. Even though it can suffer from potential immune reaction and has higher costs, they are used very successfully (5). Fragility of the grafted skin with blistering during maturation and the price are the major disadvantages.
- ❖ Recell uses similar principle, as several other commercially available materials. This approach is starting with a biopsy of the patient's healthy skin. Afterwards, a mixture of keratinocytes, melanocytes and stem cells is prepared in a liquid formulation that is later applied on burnt areas. These materials reduce the healing time in burns and may reduce the amount of necessary donor skin (6,7).
- ❖ Epidex is an engineered, fully differentiated autologous skin substitute derived from keratinocytes showing efficacy comparable to split-thickness skin grafts in wound closure and healing. It was used in a pilot study where it was possible to heal up to three-quarters of 20% of leg ulcer patients, who had no response to conservative wound care (8).

There are not many reports on the use of cultivated autografts in oculoplastic surgery and aside from the materials mentioned above we have not found any study that would assess their use in the reconstruction of the periocular region.

Nevertheless, ophthalmic plastic surgeons are generally familiar with the use of stem cells in ophthalmology. There are also some reports about the use of adipose-derived stem cells (ASCs).

ASCs are mesenchymal stem cells (MSCs) that are obtained from abundant adipose tissue. They can be expanded *in vitro*, and have the capacity to differentiate into multiple cell lineages. Obtained by minimally invasive

procedures they are promising for regenerating tissues (9). ASCs can be obtained from periocular fat and should be suitable for the use in the periocular region (5).

On the other hand, up to this date, there was no large randomized trial about ASCs in the reconstruction of the periocular region or even in periocular cosmetic surgery. Therefore, further research is much needed.

## Allografts

Generally, allografts are grafts transplanted between two genetically distinct individuals of the same species. We can distinguish three categories of allografts: epithelial/epidermal, dermal, and composites (2). The main advantage of the use of cultured allograft includes avoiding biopsy in donor (which is questionable, when taking in consideration the size and limited localization of oculoplastic defect). The principle is in the stimulation of host growth factors by the grafted keratinocytes, the graft itself is not permanent.

### *Acellular dermal allografts*

Acellular dermal allografts serve as scaffold into that host tissue integrates and revascularizes (2). There are many commercially available products—for example GraftJacket, Allomax, Alloderm, Integra, DermaMatrix. They are acellular and mostly derived from human skin and processed in the tissue banks to acellular dermis.

Acellular dermal matrix (ADM) has some tradition in ophthalmic plastic surgery, even though the bioengineered materials are not used very frequently. Most existing literature is aimed on Alloderm.

### **Alloderm**

Alloderm is considered to be an option in patients with large defects who are not eligible for classic reconstruction. There is a retrospective case series describing the successful use of Alloderm in six patients with large periocular defects during years 1997–2006 (10). Four presented with excessive defect after tumour surgery, two presented after trauma. In all patients the graft was successfully epithelized without any post-surgical complications. Unfortunately, the size of the defects was not mentioned in the text.

In an older, but bigger, retrospective study 23 patients with ADM (Alloderm) reconstruction were reported. The study group was again quite heterogeneous—applications were classified as barrier/scaffolding (lid spacer graft or primary/secondary implant coverage in anophthalmic

socket) and volume augmentation (superior sulcus and other periorbital soft tissue contour) (11). There were in total eight eyelid retraction repair, all successful. Primary coverage of polyethylene orbital implants was successful in all four cases. Secondary coverage of exposed orbital implants was successful in four out of seven cases. Augmentation surgery was all successful. The author considered acellular human dermis being an excellent barrier and reconstructive grafting. Other successful use of Alloderm in periocular volume augmentation was described by Shorr *et al.* (12).

In the retrospective paper by Bee *et al.*, the periocular region represents only minor portion of all 98 procedures in that ADM was used as an oculoplastic indication. Bee describes successful use of Alloderm for reconstruction of a periocular defect in three cases and as a soft tissue filler in the cheek and forehead area (both one case only) (13).

Despite of not being major focus of our review, we would like to mention that other retrospective studies also consider Alloderm as a good material for dealing with insufficient conjunctiva during evisceration or enucleation surgery (14).

Another retrospective review by Chang *et al.* also concentrated on the use of ADM (Alloderm) in several oculoplastic indications (15). Again, the group of interest was various—15 cases of lower lid retraction, 10 anophthalmic socket contractions, 2 superior sulcus deformities, 2 orbital implant exposures, and 2 periorbital skin defects. In this study, the size of defect was mentioned with 21×6 mm. In both patients the defects were healed without complications. However, it was not mentioned why conventional autografting was not used.

The use of ADM (dominantly Alloderm) as a spacer graft is often mentioned in literature. According to Sullivan, its contraction is much higher than in traditional hard palate grafts (16). On the other hand, another study considered both materials comparable, with hard palate grafts superior to thin Alloderm grafts (17).

There is also one study of successful usage of Enduragen® (Porcine Acellular Dermal Matrix) that showed that as a spacer this material can be successfully used in upper and lower eyelid and lateral canthus. Unfortunately, the study was retrospective and it not contain any usage in periocular defects (18).

ADM is probably the most popular type of bioengineered material in ophthalmic plastic surgery. Predominantly, Alloderm is used. Although there is no doubt that it can be successfully used in many indications, including reconstruction of the periocular region, the literature

surprisingly lacks enough evidence-based and prospective studies. This could be probably due to the low frequency of use and indication in less common diagnosis. Nevertheless, according to the published papers, the ADM can be used as an alternative to classic flaps and autografts in the management of periocular defects or periocular volume insufficiency. In most reports the success rate is high.

### ***Cellular dermal allografts***

There are also cellular dermal allografts that are composed of structural dermal scaffold and donor fibroblasts. Cellular components synthesize proteins of the extracellular matrix stimulating wound healing. However, it also means a higher risk of rejection. Examples of commercially available materials include: Dermagraft, ICX-SKN, or Transcyte.

According to Lee *et al.*, Dermagraft is an alternative to traditionally used Alloderm (19). In the retrospective study, he used it in 13 patients, but it was not used in the periocular region—it was again used for socket contraction, lower eyelid retraction and once as a graft for reconstruction tarsus in Cutler-Beard surgery. The author points out simple manipulation, longer shelf-life and no refrigeration as the advantages over Alloderm. We did not find any other report about using cellular allografts.

### **Xenografts**

Xenografts are usually porcine or bovine products that contain dermis without epidermis. They are sterilised with antibiotics, chemical antiseptics and radiation. They support healing of many types of wounds, including trauma or burns.

Examples of xenografts are EZ\_Derm, Mediskin or Integra.

### ***Integra***

There are some reports of using Integra in oculoplastic surgery. Report from Thinda *et al.* describes a successful usage of Integra in a 36-year-old female patient after car accident with large periocular wound. The defect was 8×5 cm, reaching from medial canthus to temporal region (20) (*Figure 1*).

Another report shows the use of Integra in a 7-year-old patient with xeroderma pigmentosum after excision of large periocular melanoma 35×50×20mm with a Breslow depth of 18mm in the periocular region. The defect was successfully covered and was esthetically acceptable after 6 weeks (21).



**Figure 1** Picture of Integra Bilayer Matrix Wound Dressing. Picture is used with permission of company Integra.

Chen *et al.* described successful usage of Integra Dermal Regenerate Template (inner layer of bovine matrix collagen cross-linked with glycosaminoglycans with outer protective silicone layer, that is later removed) in large traumatic periocular defects that would be too large for the primary closure. In the retrospective review of four cases, Integra was sutured to the defects with antibiotic ointment and pressure patch for the first week. After 1 month, two patients had complete closure of the wound, one patient had 80% reduction of the defect, and the last patient had 50% reduction of the size defect (22). The authors pointed out decreased surgery time and possibility of the closure of large defects as the major advantage, with higher costs of the material and possible contraction when laid over fat tissue as the possible disadvantages of the material.

We have found no more reports of using bioengineered xenografts in periocular or periorbital region in scientific databases.

### Synthetic substitutes

Synthetic substitutes are based on artificial, non-biological material. The main advantage is no risk of possible infection that can be in the biologically based material.

They are monolayer and acellular and mostly used for covering split-thickness skin grafts of partial burns. Commercial examples are Biobrane or DuoDERM.

Biobrane is standard substitute in burn patients and it is used as temporary synthetic dressing that promotes underlying tissue's re-epithelialization. DuoDERM is hydrocolloid dressing. We have not found any articles about the use of synthetic substitutes in the periocular region, except an interesting alternative to tarsorrhaphy, in that DuoDERM was used as tape over eyelids instead of

suturing. The main advantage was that DuoDERM lasted in place better than medical tape (23).

### Discussion

Bioengineered dermal substitutes are not frequently used in the periocular region. The major reason for that is probably the fact that most of the defects are relatively small, and the surgeons have plenty of surgical techniques to close them.

On the other hand, there are situations when it is not possible to close the defect with any conventional surgical technique. According to existing literature, this is mostly in big traumas or large surgical defects, especially in oculoplastic tumour surgery. For these cases, every ophthalmic plastic surgeon should be familiar with the basics of bioengineered dermal substitutes and have plan which one could be used for successful closure of the defect.

In the literature that we have searched during preparation of this review, Alloderm and Integra are probably the most popular periocular dermal substitutes in oculoplastic surgery. Unfortunately, literature lacks any prospective or large studies using these kinds of materials in oculoplastic surgery. The reason would be probably that most of the surgeries can be done using conventional techniques and therefore these materials are not used very often. Further research is needed to study the possibilities and the future of bioengineered dermal substitutes in the reconstruction of the periocular region.

### Conclusions

Dermal substitutes are useful when the conventional surgical technique would not be sufficient for any reason. They are rarely used in the periocular region and therefore there is a significant lack of literature about this topic. Nevertheless, from the existing case reports and small series we can implicate that usage of dermal substitutes in the periocular region seems to be often successful without further complications.

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