REVIEW

Acellular Dermal Matrix in Plastic and Reconstructive Surgery

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Summary
Despite significant advances in medical research, plastic surgeons still face a shortage of suitable patient tissues, and soft tissue reconstruction is no exception. In recent years, there has been a rapid boom in the use of acellular dermal matrix (ADM) in reconstructive and aesthetic surgery. ADM is incorporated into the surrounding tissue and gradually replaced by the host's collagen, thus promoting and supporting the healing process and reducing the formation of scar tissue. The main goal of this article is to provide a brief review of the current literature assessing the clinical applications of ADM across a broad spectrum of applications in plastic and reconstructive surgery.

Key words
Acellular dermal matrix • Tissue engineering • Reconstructive surgery

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Introduction

Soft tissue reconstructions are often dependent on autologous tissues as they are predominantly treated by techniques such as full and split-thickness skin grafts, local flap coverage, and free tissue transfer. However, in many cases, their application is limited by the lack of suitable patient tissues and adverse side effects, including donor site morbidity, inflammation, risk of flap/graft complications, or even failure [1,2].

In recent years, there has been a rapid boom in the use of acellular dermal matrix (ADM) in reconstructive and aesthetic surgery. ADM is a dermal graft stripped of the epidermis and all other cellular elements in order to avoid tissue rejection and graft failure [3]. These dermal replacements reduce or eliminate the need for autologous tissue grafts and minimize morbidity at the donor site. They are prepared by the process of native dermal tissue decellularization of human cadaveric donor skin (allogeneic) or mammalian skin donor sources (xenogeneic). ADM consists of intact collagen fibers and bundles, proteins, intact elastin, hyaluronic acid, fibronectin, fibrillar collagen, type VI collagen, vascular channels, and proteoglycans. It acts as a carrier that allows tissue regeneration to occur with revascularization and fibroblast outgrowth. ADM is incorporated into the surrounding tissue and gradually replaced by the host's collagen, thus promoting and supporting the healing process and reducing the formation of scar tissue as much as possible [4].

There are many commercial ADMs (Table 1) available these days (e.g. AlloDerm, DermACELL,

Table 1. Overview of common commercially available ADMs.

Product	Description	Preparation
AlloDerm	Human, non-cross-linked	Hydrate for 10-40 minutes in NS
AlloMax	Human, non-cross-linked	Hydrate for 3 minutes in NS
DermACELL	Human, non-cross-linked	None
FlexHD	Human, non-cross-linked	Rinse in NS
NeoForm	Human, non-cross-linked	Hydrate for 3-5 minutes
Integra	Bovine, cross-linked	2 minutes in NS
SurgiMend	Bovine, non-cross-linked	Hydrate for 1 minute in NS
Permacol	Porcine, cross-linked	None
Strattice	Porcine, non-cross-linked	Hydrate for 2 minutes in NS

NS = normal saline

FlexHD, Integra, SurgiMend, NeoForm, etc.), each with variations in processing, production, storage, preparation, and use [5-7]. Decellularized matrices have proven to be superior to synthetic polymers as regenerative medicine matrix scaffolds because they can retain the hierarchical complexity of native tissue. Due to the fact that decellularized matrices can maintain a complex composition, vascular network, and tissue-specific architecture, they can promote adequate wound healing and strengthen soft tissue repair [8].

In this article, we provide a brief review of the current literature assessing the clinical applications of ADM across a broad spectrum of applications in plastic and reconstructive surgery.

Decellularization protocols

The main goal of the decellularization process is to remove all antigenic material from the tissue to prevent rejection or inflammation and preserve its structure and biochemical and biomechanical properties as much as possible. There are currently several accepted methods and procedures for decellularizing harvested skin [9-11].

Physical methods include pressure, sonication, supercritical gases, heat shock (freeze-thaw cycles), and agitation in solutions to disrupt cellular components. Chemical methods are used for plasmolysis or cytolysis, disruption of cell membranes, or degradation of nuclear components. Chemical decellularization involves using hypotonic or hypertonic solutions (distilled water, > 1% NaCl solution), ionic (SDS) and nonionic detergents (Triton X-100, acids and bases, and chelating agents (EDTA). They are often used in combination with other methods to increase the effectiveness of decellularization. A notable group of chemical agents is biologically active substances – enzymes (trypsin, dispase, lipase, collagenase, DNase, etc.). Their great advantage is the specific targeting of cell-cell attachments, cell-ECM attachments, nucleic acid-protein bonds, etc.

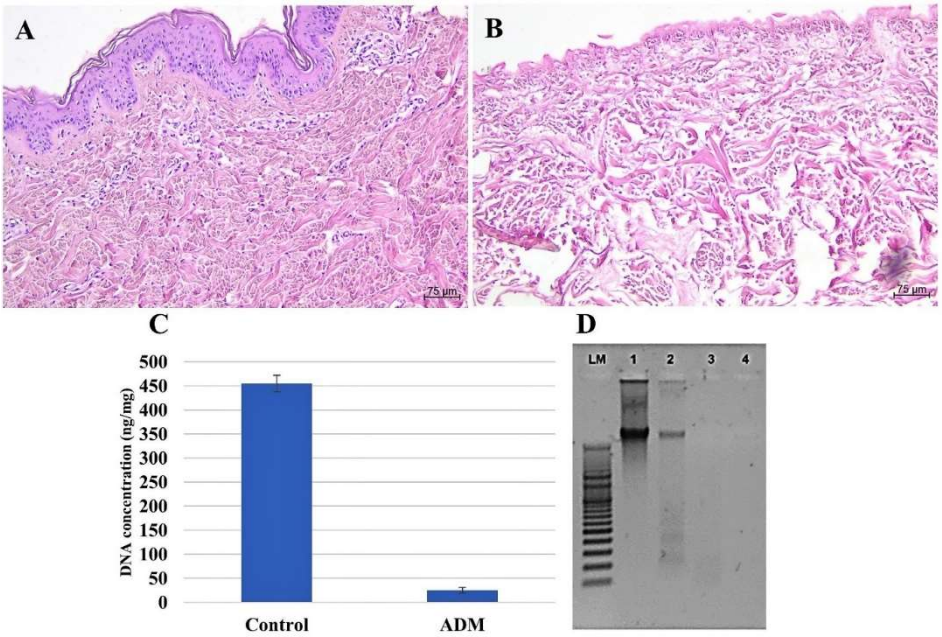

Fig. 1. HE-stained sections of native skin (**A**) and acellular dermal matrix (**B**). HE staining. The DNA concentration in ADM (**C**) and visualization of genomic DNA in 1 % agarose gel (**D**). LM length ladder, 1 allodermis, 2 H_2O 1× changed, 3 H_2O 4× changed, 4 H_2O 5× changed.

The success of decellularization is assessed by meeting three minimum criteria (Fig. 1): HE or DAPI tissue section staining with no visible nuclei, evaluating the amount of dsDNA per mg ECM dry weight (<50 ng), and the length of DNA fragments must not be larger than 200 bp [12]. The success of the decellularization process can also be verified by the method of transmission electron microscopy (Figs. 2, 3).

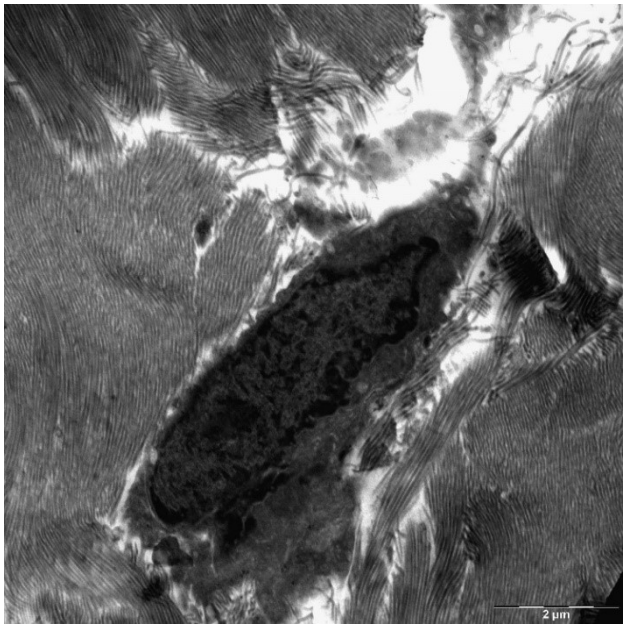

Fig. 2. Native dermis of the skin before decellularization process visualized by transmission electron microscopy. Fibroblast with predominantly euchromatic nucleus located between bundles of collagen fibers; magnification: 8900x.

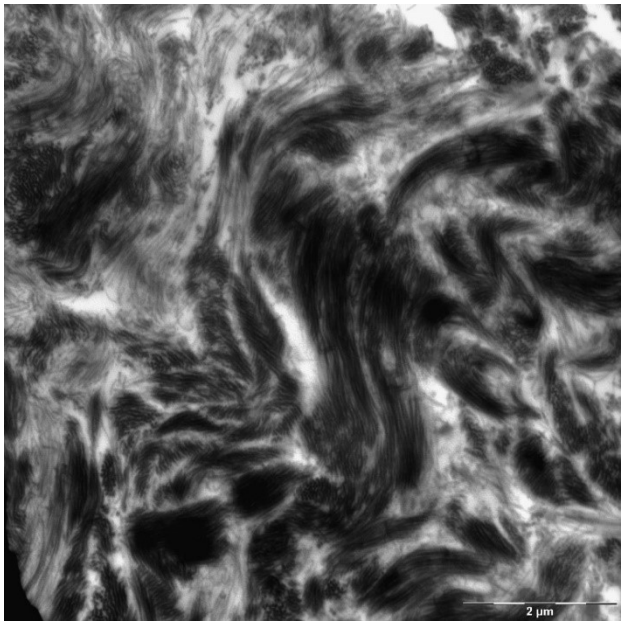

Fig. 3. Acellular dermis visualized by transmission electron microscopy; only bundles of collagen fibers are visible, but no cells; magnification: 11000x.

Acellular dermal matrix as a skin substitute

ADM can be applied in the reconstruction of soft tissues, especially in case of trauma but they are not meant to be used as full skin substitutes as they lack an epidermal layer. Although autologous grafts integrate and vascularize well, harvesting may cause donor site morbidities such as scarring, seroma, or wound dehiscence [13]. That's why the research focused on artificial replacements of the epidermis and dermis to improve functional and cosmetic outcomes and reduce the need for autologous skin transplantation. In theory, ADMs eliminate the need to harvest thick autogenous dermis and allow a much thinner graft to be harvested, reducing donor site scaring [14]. This was also confirmed in a multicenter clinical study that assessed the ability of an ADM to function as a permanent dermal transplant in full-thickness and deep partial-thickness burns [15]. At the test site, the dermal matrix was grafted to the excised wound base and a thin split-thickness autograft was simultaneously applied over it. The control site was grafted with a thicker split-thickness autograft alone. Fourteen-day take rates of the dermal matrix were statistically equivalent to the control autografts. Histology of the dermal matrix showed fibroblast infiltration, neovascularization, and neo-epithelialization without evidence of rejection. Wound assessment over time showed that thin split-thickness autografts plus allograft dermal matrix were equivalent to thicker split-thickness autografts.

Although ADMs are not widely used to cover large areas of skin loss, because ADMs require suitable conditions for integration such as a healthy vascular wound with no necrosis or infection, they have found their application in covering smaller defects or in late-stage reconstructions. Singh *et al.* [16] used ADM as a cover over the titanium mesh used for cranioplasty after craniectomy. ADM improved aesthetic outcomes by minimizing contour deformity and served as an additional buffer in the thin scalp. Gupta *et al.* [17] successfully applied ADM to correct a contour deformity in the temporal fossa after a traumatic cranioplasty.

Greaves *et al.* [18] reported increased angiogenesis in the human decellularized dermis during acute skin wound healing. Significantly increased mRNA expression of proangiogenic PROK2 and extracellular matrix protease MT6-MMP was observed only in the decellularized dermis group compared to autogenic, and xenogenic skin substitutes. Another study used ADM to treat diabetic foot ulcers (DFUs) [19]. ADM demonstrated

the ability to rapidly reduce the size of large, complex DFUs with exposed bone. Some wounds did not completely heal by 16 weeks; however, the significant reduction in size suggests that these large, complex wounds may heal if given more time.

Acellular dermal matrix in head and neck reconstruction

Bing *et al.* [20] used ADM for the treatment of nasal mucosal defects. A total of 31 patients with bilateral chronic sinusitis (maxillary sinusitis and ethmoid sinusitis) underwent nasal surgery and nasal mucosal repair. They divided the nasal cavities of each patient into control and acellular dermal matrix groups, and randomly selected one side for nasal mucosal repair by surgery. A suitable acellular dermal matrix size was selected according to the defect in each patient, placed on the wound surface, and filled with a gelatin sponge. All patients were followed up for 14 weeks to compare nasal mucosal epithelialization between the control and acellular dermal matrix groups. They observed no obvious complications or adverse reactions after nasal surgery. The acellular dermal matrix provided a growth framework for the healthy mucosa on the wounded surface and reduced postoperative epithelialization time of eight weeks in the acellular dermal matrix groups versus 14 weeks in the control group. Many surgeons have also successfully used ADM in various approaches to nasal reconstruction, such as septal perforation and correction of nasal deformities in primary and secondary rhinoplasty and septoplasty [21-23].

The broad applicability of ADMs has also been studied in skull base reconstruction. Zhong *et al.* [24] conducted a retrospective study where ADM was compared with turbinate flap (TF) in the intraoperative repair of cerebrospinal fluid (CSF) rhinorrhea in skull base tumor resection. 46 patients had undergone nasal endoscopic resection of a skull base tumour and repair of CSF rhinorrhea was retrospectively analysed. The patients were divided into ADM and TF groups according to the difference in repair materials used. The use of the ADM for patients with CSF rhinorrhea showed comparable results in terms of postoperative outcomes compared with the use of TF. ADM can serve as a safe and feasible alternative even if the flap is not available and be adequate coverage of the resultant defect. Similarly, a retrospective comparative study was conducted to assess the effectiveness of ADM as an alternative to autologous fascia lata graft for achieving skull base closure in endoscopic endonasal approaches (EEA) [25]. The authors suggested that ADMs provide a non-inferior alternative to traditional autologous fascia lata grafts for watertight closure of the skull base after EEA, potentially reducing the need to harvest a fascia lata graft. Another retrospective study also used ADM for skull base reconstruction during endoscopic skull base surgery [26]. The implant was subsequently explanted for histological analysis during revision surgery eleven to seventeen months later. The authors confirmed tissue revascularization by histological analysis. It is believed that successful revascularization is likely responsible for low infection rates, effective skull base repair, and prevention of postoperative cerebrospinal fluid leakage.

Acellular dermal matrix in breast reconstruction

In breast surgery, the utilization of ADM began in correction surgeries of visible implant rippling and symmastia [27,28]. Later on, it was also used in immediate breast reconstruction with implants [29]. Bindingnavele *et al.* [30] applied ADM in expansive postmastectomy breast reconstruction. Their results showed that this approach had an extremely low complication rate and resulted in good cosmetic outcomes.

Also, our group, in a previous study, applied ADM in 22 patients undergoing delayed post-mastectomy breast reconstruction, which resulted in a good outcome. Post-operative complications occurred only in 3 patients including one expander infection, one expander extrusion, and one expander pocket disfiguration. Moreover, histological analysis of tissue samples has confirmed the incorporation of the acellular dermal matrices into the surrounding connective tissue without any noticeable immune reaction [31]. In a more recent study, Gwak *et al.* [32] presented improved aesthetic results using human ADM as a filler in breast-conserving surgery.

ADM mainly serves to cover the lower part of the implant in submuscular placement and thereby creates support for the lower pole of the breast. It also serves as a prevention of capsular contracture. However, the possible postoperative complications with the use of ADM are still discussed. A retrospective study of 415 cases of immediate breast reconstruction with an implant showed an association between the use of ADM and an increased risk of seromas and infection. This obstacle can be overlapped by careful patient selection, choice of tissue

expander/implant volume, and post-surgery management [33].

Nowadays, there are plenty of ADM types, which are used in breast reconstruction. The best known of them and the most studied is AlloDerm, with more than 900 publications available on PubMed database (National Center for Biotechnology Information, at the U.S. National Library of Medicine, located at the National Institutes of Health). However, each ADM preparation application has a different biological response after being inserted into a living organism. For instance, in our previous study, we described the histology of one unusual type of metaplasia that resulted in the formation of a synovial-like membrane typical of joints within a female patient's breasts around silicone implants [34]. Even though ADM is used worldwide in more than 60 % of breast reconstructions using implants, thus largely replacing the more "traditional" reconstruction technique using implants with partial or complete coverage of the implant by the muscle [35]. On the other hand, there is a debate regarding the durability of the mechanical integrity of the ADM in this indication. However, questions regarding the long-term follow-up and safety profile of ADM need to be answered in the future.

Acellular dermal matrix in vaginal reconstruction

Reconstruction of the vagina after delivery seems to be a new surgical approach because this condition interferes with normal genital function and may lead to decreased sexual satisfaction, and secondary psychological disorders [36,37]. Ward and colleagues conducted a study to evaluate the effectiveness of vaginal reconstruction using AlloDerm. They revealed good subjective success, despite a moderate rate of objective failure within the first 24 months [38]. Similarly, Clemons *et al.* [39] also described promising results of a technique of vaginal paravaginal repair that used ADM in women with recurrent stage II or with primary or recurrent stage III/IV anterior vaginal wall prolapse. Mentioned studies significantly support the idea of using ADM in vaginal reconstructions.

In a more recent study, Karon *et al.* [40] introduced the application of ADM in gynecologic laparoscopic surgery. They demonstrated that this approach is safe, less invasive, and may bring good outcomes in about 85% of treated women. Moreover, they conclude that the application of ADM is comparable with results obtained with polypropylene mesh but without erosion complications. This makes the ADM a good alternative in laparoscopic sacrocolpopexy. However, further research should be considered in this medical branch.

Conclusions

Tissue-engineered skin substitutes emerged in the 1980s. The development was mainly motivated by the great need and critical lack of material that would be suitable for early coverage of extensive injuries in patients with insufficient sources of autologous soft tissues for grafting. Since then, ADMs have been extensively studied with respect to application in various reconstructive and aesthetic surgeries. However, there is still a need for additional research into new applications of ADM in reconstructive surgery and further studies have to be performed to improve reconstruction approaches with the use of ADM.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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