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# The Use of Dermal Substitutes in Burn Surgery: Acute Phase

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## Abstract

Dermal substitutes are increasingly becoming an essential part of the burn care strategy. During the acute phase of burn treatment, dermal substitutes improve functional and cosmetic results long-term and thus increase quality of life. In the chronic wound setting, dermal substitutes are used to reconstruct and improve burn scars and other defects. Despite some successes in the use of dermal substitutes there are more needs and requirements to further improve outcomes and hence further research is required not only to strengthen scientific evidence regarding their effects but also to develop new technology and products. Dermal substitutes also emerge as pivotal research strategies to develop adequate scaffolds for stem cells, tissue engineering and regenerative medicine applications to obtain long-lasting and scarless artificial skin. This review discusses status-quo of dermal substitutes and novel strategies in the use of dermal substitutes with a focus on burn care.

### Keywords

dermal substitute; burn acute surgery; tissue engineering

## INTRODUCTION

Dermal substitutes are becoming more and more an essential part of burn care. During the acute phase of burn treatment, dermal substitutes improve functional and cosmetic results long-term and thus enhance quality of life. In the chronic wound setting, dermal substitutes are used to reconstruct and improve burn scars and other defects. Despite the potential and need of dermal substitutes, further research is required not only to strengthen scientific evidence regarding their effects but also to develop new technology and products. Furthermore, dermal substitutes also emerge as pivotal research strategies to develop adequate scaffolds for stem cells, tissue engineering and regenerative medicine applications to obtain long-lasting and scarless artificial skin.

### 1. DEFINITION OF DERMAL SUBSTITUTES

Dermal substitutes are bio-matrices that fulfil the functions of the cutaneous dermal layer: control of pain and scarring. They act as matrices or scaffolds and promote new tissue growth and enhance wound healing (1, 2), with enhanced pliability and a more favourable

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scar. Dermal substitutes play a major role in repairing full thickness skin defects, both in acute and chronic wounds (3), and there is evidence that they improve scar quality (4).

## 2. HISTORY OF DERMAL SUBSTITUTES

Advances in acute treatment, acute care and intensive care have resulted in decreased mortality in major burns (5). The current focus in burn care has now shifted towards improving the long-term function and appearance of the healed skin in conjunction with quality of life (6). The loss of the dermis in extensive full thickness wounds like burns poses a serious problem, which is not completely solved by the application of split-thickness autograft (7). It is important to have an effective *dermal* replacement because dermal tissue does not regenerate into normal dermis *in vivo* after full thickness dermal injuries. Application of a dermal substitute underneath the autologous skin graft may improve the wound healing process (8) in the treatment of burns, skin ulcers, various deep wounds, and unstable scar replacement (3, 4, 7). In addition, dermal substitutes play a role in control of scarring (2). Pathologically excessive scar formation (i.e. hypertrophic scars and keloids) represents a significant morbidity in surviving burn patients. The prevalence is variable and can be up to 67%, and this increases with increasing time to heal the wound (9). Hypertrophic/Keloid scars pose several problems both aesthetically and functionally (due to contracture formation). They may also lead to the formation of carcinoma e.g. Marjolin's ulcer (10). These patients with keloids or also suffer from impairment of their quality of life, causing physical, psychological, and social sequelae (11).

## 3. DESIGN CONSIDERATIONS

**FUNCTIONAL REQUIREMENTS OF DERMAL SUBSTITUTES—**Dermal substitutes are designed to mimic the basic properties of the extracellular matrix (ECM) (4), and should share the same functions as normal dermis:

1. Restoration of skin anatomy and physiologic function: Due to their scaffolding properties, dermal substitutes help to control pain, contracture, and scarring, with reduced healing times (3). If the dermal substitute is provided with an impermeable wound cover, like a silicone layer, it can also function as a protection of the wound from infection and fluid loss. The vascularization period of the dermal component is usually 21 days, and it correlates with wound infection rates. After that, the silicone layer is removed and replaced by an autologous split-skin graft. This procedure is known as the two-step procedure (e.g. Integra®, see below for further description). To avoid infection and two operations, an advantageous method has been developed: immediately after debridement, the dermal substitute is placed in the wound and covered by an autologous split-skin graft (e.g. Matriderm® or Integra single layer®). This method provides earlier wound closure but may hamper graft survival, and not all dermal substitutes are compatible with this one-step procedure as it is dependant on pore size and influx of cells (3).

2. **Biocompatibility:** tissue integration, host tolerance or immune-compatibility and biodegradation. Biocompatibility is demonstrated by the in-growth of fibroblasts and blood vessels (6). Vascularization of the substitutes is mandatory to enhance the rate of split-skin graft take (11). Apart from rapid adherence and vascularization, other related factors to take into account are mechanical stability and durability. Biopolymers may be tissue-derived or synthetic (12). The biopolymers in use range from collagen (the most popular one), hyaluronic acid, fibrin, laminin, and elastin, polylactic acid (PLA), to polyglycolide (PGA), (4). When using natural materials (allogeneic or xenogeneic), immunogenicity and disease transmission (for instance, prion disease and porcine retroviruses in xenograft products (13) remain a concern (4). The use of synthetic materials has in

some cases been found to lead to a foreign body response and fibrous capsule formation. Therefore, controlled rate of biodegradation; non-toxic metabolites; low or absent antigenicity, inflammatory or foreign body reactions (14) are mandatory. Synthetic materials are also more cost-effective than the natural ones.

3. Hosting or enabling the influx of cells that will function as dermal cells: the composition, pore size, and degradability of the dermal substitute facilitate the invasion of normal fibroblasts and capillaries to synthesize new dermis (14, 15). Although a scaffold material can be designed as "permanent", generally it is considered desirable that the transplanted scaffold be safely assimilated into the body as new matrix is generated by the populating cells (4).

4. **Resistance to shear forces:** The dermal substitute should be strong enough to be held in place in difficult anatomic areas such as joints (11).

## FUTURE DIRECTIONS

Regarding current bioengineered skin substitutes, to date there is still none that replaces the skin in its entirety (functionally or morphologically). Furthermore, although dermal substitutes have achieved some clinical success in restoring damaged skin, some milestones may still remain to be achieved: such as decreasing or abrogating prolonged healing times and scarring without skin appendages; objectively proving that they improve cutaneous scars in comparison to the use of split-thickness graft alone; the need for a second surgery, and limited tissue functionality and high cost.

As dermal substitutes lack the epidermal component necessary for restoring fully functional skin, on going research is devoted to developing combined dermal-epidermal bio-engineered cultured skin substitutes and, most recently, stem cell therapy and tissue engineering (16, 17) (Table 1). Dermal substitutes may serve as a three-dimensional scaffold to host stem cells and be programmed to accelerate wound healing with minimal fibrosis, eventually improving function and cosmetics.

### 4. CLASSIFICATION OF DERMAL SUBSTITUTES

Current literature categorizes dermal substitutes based on the source of the dermal substitute, as synthetic versus biological materials. The latter are further divided between natural, and constructed or artificial materials (3, 11). In the classic literature, "natural" materials would only refer to "natural biological" materials.

## BIOLOGICAL MATERIALS

### NATURAL BIOLOGICAL MATERIALS

Natural biological materials consist of human (the gold standard) or porcine tissue, which is treated to obtain an acellular scaffold (3). Cells are eliminated to decrease the risk of immune responses (6). At the same time, natural dermal substitutes have the optimal qualities in terms of porosity, micro-topology and presence of basement membrane (18, 19). However, it is very difficult to entirely remove all cell remnants. This drawback, in addition to the risk of disease transmission, enforces the use of these materials as temporary dressings, rather than permanent dermal substitutes (3). However, their main advantages are:

a. High similarity to native dermis (specially when glycerol-sterilization is used (20)) because they provide a 3D-ECM of collagen and elastin without cells (11) with theoretical less risk of excessive scarring

b. Partial conservation of basement membrane (3), which favours keratinocyte adherence (21) (Table 2).

## HUMAN-DERIVED NATURAL BIOLOGICAL MATERIALS

### ALLODERM®

Alloderm® (LifeCell Corporation, Woodlands, TX) is human cadaver skin that has been chemically treated to remove all cellular material in the dermis and is one of the oldest and most utilized matrices (22). It is processed from fresh cadaver skin treated with high salt to remove the epidermis and extract the cellular material. After a freeze-dry step, the immunologically inert acellular dermal matrix with intact basement membrane complex is obtained. Following its application to a wound bed, it is repopulated by host cells, revascularised and becomes incorporated into the tissue (23). Therefore, it functions as a template for dermal regeneration. Approved and considered as banked human tissue by the FDA, it has been used to treat burns since 1992, and it has also been used to treat severe soft tissue defects. This product has been shown to have good graft take rates and to reduce subsequent scarring of full-thickness wounds, with results similar to Dermagraft® (23), even though the graft take of split-skin grafts over the former one in a one-step procedure was lower than split-skin graft applied alone (24). In summary, there are many advantages of this human-derived natural biological material: it is acellular and immunologically inert; it provides a template with natural dermal porosity for regeneration with the presence of an intact basement membrane and it allows the use of thinner autograft. The disadvantages include risk of transmitting infectious diseases, the need for two surgical procedures, high cost and donor site (24, 25).

### GLYADERM ®

Glyaderm® (Glycerol-preserved acellular dermis) is a novel dermal substitute, produced and distributed by Euro Skin Bank in the Netherlands. It is an acellular dermal collagen-elastin matrix obtained from human donorskin, preserved in 85% glycerol (specifically, a NaOH treated glycerol preserved cadaver skin (6). It is 0.3mm in thickness, and it is best used in a two-step procedure. This human-derived natural biological material is currently under a European multicentre burn unit clinical trial.

This dermal substitute is recommended to be used 5 or 7 days after wound debridement and allograft coverage, to assure an appropriate wound bed. In the two-step procedure, after 5-7 days, a meshed split-thickness skin graft is applied on top of it (26).

Application of glycerol-preserved acellular dermis in a two-step procedure, allowing the dermal substitute to become well vascularized before skin graft application, resulted in better take rates and reduced wound contraction compared to control wounds treated with only split-skin grafts, similar to Alloderm® (3).

Experiments performed by Pirayesh, et al., indicated that the rate of skin graft take was reduced when applied as a one-step procedure on top of glycerol-preserved acellular dermis or acellular human cadaver dermis in a porcine full thickness wound model (3). Compared to acellular human cadaver dermis, glycerol-preserved acellular dermis offers a more cost-effective method to eliminate the dermal antigenic structures (6).

## PORCINE-DERIVED NATURAL BIOLOGICAL MATERIALS

Porcine dermal matrices are very similar to human dermal matrices, and although they have the disadvantages of any xenograft, they represent the first choice of non-human-derived natural biological dermal substitutes (27). Many researchers consider them as a substitute for acellular human dermal matrices in the future (28). Currently, there are three acellular porcine dermal matrices in the market: Permacol® (used in full-thickness defects such as burns and for soft tissue reconstruction, such as hernia repair), Strattice® and Xenoderm®.

## CONSTRUCTED OR ARTIFICIAL BIOLOGICAL MATERIALS

These materials contain designed, controlled and purified biological molecules (mainly collagen) by means of lyophilisation, which can be supplemented and cross-linked with glycosaminoglycans (GAGs) in order to modulate its properties (29), reducing immune rejection and improving the composition of the matrix with specific growth factors. Disadvantages include: the lack of complete knowledge of the material, which should be incorporated or avoided, and also they do not mimic native dermis in its entirety (there is usually absence of basement membrane and there is varying architecture) (3) (Table 3).

### INTEGRA ®

Integra® (Integra Life Science Corporation, Plainsboro, NJ, USA) artificial skin is currently the most widely accepted artificial skin substitute (23), for acute deep partial-thickness and full-thickness burns, and for burn reconstruction (14, 30). Furthermore, this product has also been used for chronic non-healing wounds and for reconstruction of cutaneous lesions, even with bone exposure, and to fill in soft-tissue defects in reconstructive and aesthetic surgery (31-34). This dermal substitute was introduced in 1981 by Yannas and Burke (14, 35, 36), and has been approved by the FDA for use in burns and for unstable scar replacement (10, 36).

This product comes in two forms: the original bilayer and a single layer (IntegraSL®) form. It is composed of a cross-linked bovine tendon collagen-based dermal matrix linked with glycosaminoglycans (GAG) (23, 25, 35, 37, 38). The bilayer has an outer layer or membrane composed of silicone (synthetic polysiloxane polymer or silastic) (38), which works as a temporary epidermis and serves to control moisture loss from the wound (10, 37, 39). In fact, water flux across this silicone membrane is the same as that across normal epidermis, 0.5 ml/cm$^2$/hr (40). This superficial silicone layer is imbedded with monofilament nylon sutures to easily distinguish it from the collagen dermal layer (35). The dermal layer contains many pores, and it is manufactured with a defined degradation rate and controlled porosity (7). An appropriate pore size is critical to allow the optimal in-growth of patients' own fibroblasts and endothelial cells, and is carefully controlled at 50 +20 ~tm (39) or 70-200 micrometres (23). Larger pores prevent the cell migration process and smaller pores delay bio-integration (23). Freeze drying procedures are used to control pore size (3).

The collagen dermal replacement layer serves as a matrix for the infiltration of fibroblasts, macrophages, lymphocytes, and capillaries derived from the wound bed. As the healing progresses, an endogenous collagen matrix is deposited by fibroblasts; simultaneously, the dermal layer of the artificial dermis is degraded, usually in approximately 30 days (39, 41). The degradation rate of the collagen-GAG sponge is controlled by glutaraldehyde-induced cross-links (38, 39). Upon adequate vascularization of the dermal layer and availability of donor autograft tissue, usually in 21 days (although it has also been described in only 10-14 (39) or even up to 8 weeks (23, 35), the temporary silicone layer is removed and an ultra-thin, possibly meshed split-skin autograft is placed over the vascular "neodermis".

The formation of the neo-dermis leads to improved scar cosmetic appearance and elasticity when compared to SSG alone [Nguyen et al. 2010], with good aesthetic and functional outcomes (34, 37, 42). It also allows for vascularization in poor recipient sites, such as areas over exposed bone or tendon (32). Furthermore, it allows for the use of thinner grafts, resulting in more rapid healing of donor sites and decreased hospital stay (43). Its design also allows for ease of use given its immediate availability and shelf storage (43). Despite the benefits of this dermal substitute and its use worldwide, there is still paucity of scientific evidence for its use (37, 43).

The main complication appears to be collection of hematomas and seromas beneath the product, which increases its susceptibility to infection (35, 37), however this can be prevented by careful surgical technique (39). As this dermal substitute has no intrinsic antibacterial qualities, careful wound preparation with an antiseptic wash and meticulous haemostasis is essential.

The scientific literature describes a Proflavin wool tie-over dressing and prophylactic courses of oral Flucloxacillin or Erythromycin (if allergic to Penicillins), antiseptic irrigation catheters above the dermal substitute sheet, washes in Diflucan, Meropenem and Vancomycin with an overlying Acticoat® dressing (Smith & Nephew, UK), and the use of V.A.C. negative pressure dressing (34). Infection may be subtle and amenable to needle aspiration but again relies on regular dressing reviews and experience. Indeed, regular follow-up and wound assessment, as well as continuity of care by a core specialist team is vital in ensuring optimum outcomes (34).

A minor disadvantage is separation of the silastic membrane at the periphery, which is not so serious problem (39). Other disadvantages include the relatively high cost, relative difficulty of use (with the need for sequential operative procedures) and the risk of (animal) virally transmitted diseases. Social, cultural, and ethical problems may arise as well, because of animal tissue components (43). Furthermore, this dermal substitute must be avoided in patients that have developed allergic reactions to bovine products (36).

The inability to replace the dermal and epidermal layer simultaneously, due to the lack of real and permanent epidermal components (25) is the main disadvantage of this popular dermal substitute.(Table 4).

## MATRIDERM ®

Matriderm® (Skin and Health Care AG, Billerbeck, Germany) is a multiporous membrane from bovine origin, composed of collagen (types I, III and V) and a hydrolysate of elastin-alpha, treated with gamma rays (35). Its function is to enhance skin elasticity and improve the resulting scar quality in wounds, especially in the case of burns (44-48).

As with the previously artificial biological material, this one is utilised for dermal regeneration, and its indications are similar. It also has two forms, 1mm and 2mm thickness, requiring either a single-stage or a two-step procedure, respectively. In contrast to current most used Integra®, Matriderm® is usually used in single stage procedures (47). The bilayer form of the former one contains chondroitin-6-sulfate, which has antigenic properties, in contrast to elastin. This explains why it requires up to 3 weeks to become fully vascularized, in contrast to this other artificial biological material, which can have a split-skin graft applied in a one-step procedure.

This bovine collagen-elastin dermal substitute serves to treat soft tissue defects, full thickness or deep dermal burns, and chronic wounds, but especially those located in cosmetic and functionally important areas, such as hands or joints (44). It is especially useful in the pediatric population to enhance scar quality. This artificial biological material has been shown to accommodate immediate split thickness skin grafting with no diminished take (49) and appears to be feasible for use in critically ill patients in a one-stage procedure (44). The matrix serves as a support structure for the in-growth of cells and vessels; its elastin component improves the stability and elasticity of the regenerating tissue. In fact, elastin-based dermal substitutes have the potential to decrease wound contraction and improve scar appearance and functionality (48).

As the healing process advances, fibroblasts deposit native extracellular matrix as the material resorbs (45). Schneider et al. (2009) compared the engraftment rate and vascularisation of the two main used artificial biological materials in a rat model, finding no major differences between the two (46).

In experimental models, the matrix composition of this bovine collagen-elastin dermal substitute reduces wound contracture. In a porcine full-thickness wound model, elastin-coated collagen matrices reduced granulation tissue formation, fibrosis, and contraction, and stimulated collagen deposition by fibroblasts (3). Clinical trials with a long-term clinical evaluation showed no difference in scar elasticity between the described dermal substitute and split thickness grafts alone (49). However, there is still lack of clinical data on the development of wound contracture and weak scientific evidence. The advantages and disadvantages of this product are summarised in Table 5.

### HYALOMATRIX ®/ HYALOGRAFT 3D ®

Hyalomatrix® (Anika Therapeutics, former Fidia Advanced Biopolymers, Padua, Italy) is a bilayer, esterified hyaluronic acid (Hyaff) matrix or scaffold with an outer silicone membrane. The scaffold delivers hyaluronan to the wound bed, allowing cellular invasion and capillary growth, being promptly colonized by fibroblasts and ECM components (50), and is biodegradable. The silicone membrane acts as a temporary epidermal barrier (51). This dermal substitute allows wound closure via spontaneous re-epithelialization, and can also act as a suitable dermal layer for skin grafting

[(http://www.anikatherapeutics.com/products/dermal/hyalomatrix.html)]. It is indicated in traumatic, burn, and chronic wounds

[http://www.accessdata.fda.gov/cdrh_docs/pdf7/K073251.pdf]. Hyalograft-3D® is a variant of the product, which incorporates autologous fibroblasts. This latter material is not currently available for sale in the USA.

[http://www.anikatherapeutics.com/products/dermal/hyalomatrix.html].

## SYNTHETIC MATERIALS

### DERMAGRAFT ®

Dermagraft® (Advanced BioHealing, LaJolla, CA, USA) is a bio-absorbable polyglactin (vicryl) mesh seeded with cryo-preserved neonatal allogeneic foreskin fibroblasts (36, 52), using the Cooper method (53). It does not contain macrophages, lymphocytes, blood vessels, or hair follicles (38). This fibroblast collagen matrix can be used alone, or as a base for meshed split-thickness skin autograft or epidermal cultures (54), and as a temporary or permanent covering on excised burn wounds (52, 55). Indications for the usage of this dermal substitute are in burn wounds, chronic wounds and diabetic ulcers (3). It is advised that this material should be used in patients that have adequate blood supply (38). Its use in diabetic ulcers remains controversial, even though this fibroblast-collagen matrix was primarily marketed for stimulating the healing of chronic lesions, rather than for closing burn wounds (23).

This dermal substitute appears to produce results as good as allograft with regard to wound infection, wound exudate, wound healing time, wound closure, and graft take. It is more readily removed than allograft, with significantly higher level of patient satisfaction (3, 56). There have been no reported adverse reactions to Dermagraft®, with no evidence of rejection, early deterioration, or separation from wound [Hansbrough et al. 1997]. To date there has been no safety issues regarding this material (57).

The advantages of this skin substitute include good resistance to tearing, ease of handling, and lack of rejection (58).

ATS filed for bankruptcy in 2002 (59) and was acquired by Smith and Nephew, and was then closed. Although Transcyte® and Dermagraft® are currently off the market, these technologies have been licensed to Advanced BioHealing for further production and marketing to improve the product.

### TRANSCYTE ® (Dermagraft-TC ®)

Transcyte is a temporary, synthetic covering composed of a semi-permeable silicone membrane and an extracellular matrix of newborn human dermal fibroblasts cultured on a porcine collagen-coated nylon mesh (2) (similar to a Biobrane® seeded with fibroblasts (35)).

It is a laboratory-grown temporary skin replacement (25), produced originally by Advanced Tissue Sciences Inc (ATS, La Jolla, CA) (36), which was later acquired and transferred to Smith & Nephew, Largo, FL, USA (38). Human neonatal foreskin (allogeneic) fibroblasts are cultured and proliferate on an inner nylon mesh of fibres that are embedded in an outer silastic layer for 4 to 6 weeks (25, 36) forming a dense cellular tissue which contains high levels of secreted human matrix proteins as well as multiple growth factors (58). A multicentre, randomized, controlled, paired within patient study in 66 patients with 132 excised burn wounds showed this skin substitute to be as effective as human cadaver skin and was successful as a temporary wound coverage after excision of the eschar from burn wounds (56). This fibroblast-collagen-nylon-silicone mesh is US FDA-approved for the treatment of burn wounds (it was the first human-based, bioengineered temporary skin substitute for the treatment of excised full-thickness and partial-thickness burns approved by the US FDA in 1997 (38), and advantages include immediate availability, ease of storage (25) and direct visual monitoring of the wound bed (due to transparency) (38).

It has been indicated for use as a temporary covering for excised burns prior to autografting or burns that do not require autografting (partial thickness burns). This material is applied to the burn and will peel away as the burn heals (2) or it must be removed or excised prior to grafting full-thickness wounds.

## 5. Summary

Dermal skin substitutes have become an important part of acute and long-term burn care (60). However, at present there is still no ideal dermal substitute that completely mimics the morphology and functions of skin. Furthermore, although there are reports in literature of better cosmetic and functional outcomes with their use in burns, scientific evidence is still scarce, and further research is warranted. Indeed, regenerative medicine and the application of tissue engineering to design appropriate scaffolds for application of stem cells appears to be the future of dermal and skin substitutes.

Finally, interdisciplinary cooperation between basic researchers, clinicians, and surgeons is mandatory to develop the ultimate skin substitute, which will allow for reduction in the morbidity and mortality of burn patients and improvement in their quality of life.

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**Table 1**

New dermal substitutes: tissue-engineered scaffolds with stem cells [Hodgkinson and Bayat 2011]

| |
|---|
| The most successful scaffolds are acellular polymer matrices, prepared through lyophilization and phase separation techniques, designed to mimic the dermal extracellular matrix. |
| Cell-containing scaffolds have short shelf life, high cost, and low viability of transplanted cells. |
| However, the use of stem cells within substitutes containing 3D scaffolds or microenvironments that control stem cell behaviour may decrease cell death and lead to new-generation dermal substitutes. |

## Table 2

Natural biological materials' characteristics.

| **Risks** | **Currently used Solutions** | | |
|---|---|---|---|
| | **Types** | | **Similarity to native dermis?** |
| **Disease transmission** | Sterilization | Ethylene-oxide | No |
| | | γ-irradiation | No |
| | | Glycerol | Yes |
| **Immune rejection** | Decellularization | NaCl-SDS | Yes |
| | | NaOH | Yes * |

* But it decreases basement membrane.

**Table 3**

Constructed biological materials:

| Design characteristics | Advantages | Disadvantages |
|---|---|---|
| **Cross-linking** | Stability*<br>Increases matrix longevity in the wound area. | Foreign body response<br>-Less split-skin graft take rate<br>-More contraction and HS risk<br>Increased matrix rigidity<br>Reduce cell viability |
| **GAGs** | Increase collagen resistance to collagenases.<br>-Avoid excessive cross-linking | Many GAGS (as chondroitin-6-sulphate) are anti-angiogenic |

Abbreviations: HS = Hypertrophic Scarring; GAGs = Glycosaminoglycans.

*Stability of collagen dermal substitutes can also be increased by adding fibronectin, hyaluronic acid, or elastin.

**Table 4**

Advantages and disadvantages of Integra®: [Muangman et al. 2006; Fette 2005]

| **Advantages** | **Disadvantages** |
|---|---|
| 1. No immune reaction | 1. Collection fluid risk (hematoma, infection, seroma) |
| 2. No histological harm | 2. Virus and prion-transmission risk |
| 3. Thinner epidermal grafts and smaller mesh possible | 3. 2-step operational procedures (in the bilayer or classical form) |
| 4. Better aesthetic and functional outcomes (less itching, less hypertrophic scarring rates, better movements)* | 4. High cost |
| 5. Immediate availability | 5. Steep learning curve |
| 6. Prolonged shelf time; off-the-shelf product | 6. Inability to replace both dermal and epidermal components. |
| 7. Capable of vascularizing over exposed bone and tendon | 7. Still weak scientific evidence* |

**Table 5**

Advantages and disadvantages of Matriderm®: [Haslik et al. 2010]

| Advantages | Disadvantages |
|---|---|
| One-step procedure | Still weak scientific evidence |
| Better cosmesis and elasticity | |
| Off-the-shelf product | |

**Table 6**

Classification of dermal substitutes.

| MATERIALS | COMPOSITION/LAYERS | THICKNESS | INDICATIONS | BRAND |
|---|---|---|---|---|
| **Natural biological materials** | | | | |
| **Alloderm** | Acellular human cadaver dermis | 0.79-3.3 mm | Burn wounds, soft tissue replacement | Lifecell Corporation, Branchburg, NJ, USA |
| **Glyaderm** | Acellular human dermis | 0.2-0.6 mm | Full-thickness wounds | Euro Skin Bank, Beverwijk, Netherlands |
| **Graftjacket** | Acellular human dermis | 1, 1.4 or 2 mm | Chronic wounds, ligament repair, soft tissue replacement | Wright Medical Technology, Inc, Arlington, TN, USA |
| **DermaMatrix** | Acellular human dermis | 0.2-1.7 mm | Soft tissue replacement | Synthes, West Chester, PA, USA |
| **AlloMax (formerly "NeoForm")** | Acellular human dermis (collagen + elastin) | | Soft tissue repair | Bard Davol |
| **Tiscover** | Acellular human dermis with autologous fibroblasts | 1-2 mm | Chronic wounds | A-SKIN B.V., Amsterdam, Netherlands |
| **SurgiMend** | Acellular bovine dermis | 0.4-1.54 mm | Soft tissue reconstruction | TEI Biosciences, Boston, Mass |
| **Strattice** | Acellular porcine dermis | 1.5-2 mm | Soft tissue reconstruction | LifeCell, Branchburg, NJ |
| **Permacol** | Acellular porcine dermis | 0.4 or 1.5 mm | Full-thickness wounds | Covedien, Mansfield MSA |
| **Xenoderm** | Acellular porcine dermis | | Full-thickness wounds | MBP (Asclepios Medizintechnik), Neustadt, Germany |
| **Oasis (burn matrix)** | Porcine small intestine submucosa acellular collagen matrix | 0.15- 0.30 mm | Burn and Chronic wounds | Healthpoint Ltd, Fort Worth, TX, USA |
| **Artificial biological materials** | | | | |
| **Integra** | Bilayer:<br>1.Human collagen I with GAG<br>2.Silicone<br>(There is a single layer integra with no silicone) | 1.3 mm | Burn wounds, chronic wounds, soft tissue defects | Integra life Sciences Corp, Plainsboro, NJ, USA |
| **Matriderm** | Bovine collagen I + elastin | 1 or 2 mm (2 forms) | Burn and chronic | Skin and Health Care |

| MATERIALS | COMPOSITION/LAYERS | THICKNESS | INDICATIONS | BRAND |
|---|---|---|---|---|
| | | | wounds | AG, Billerbeck, Germany |
| **Terudermis** | 1. Calf collagen<br>2. Polyester mesh<br>3. Silicone<br>(There is a monolayer type with only collagen) | | Burn and other traumatic and mucosal defects | Olympus Terumo Biomaterials Corp. |
| **Hyalomatrix** | Hyaluronan based scaffold with autologous fibroblasts | 1.2 mm | Burn and chronic wounds | Fidia |
| **Transcyte** | 1. Collagen with neonatal fibroblasts<br>2. Nylon mesh<br>3. Silicone | | Burns | Advanced Tissue Sciences, Inc. La Jolla, California, USA |
| **Apligraf*** | 1.Bovine collagen I gel with allogeneic neonatal fibroblasts<br>2.neonatal keratinocytes | 0.4 – 0.75 mm | Burn and chronic wounds, skin graft donor sites, epidermolysis bullosa | Organogenesis, Canton, MA, USA |
| **Orcel (Formerly "Composite Cultured Skin")** | Collagen I sponge + gel with allogeneic fibroblasts and keratinocytes | 1 mm | Chronic wounds, skin graft donor sites | Forticel Bioscience |
| **Renoskin** | Bovine collagen I with GAG | 1.5-2.5 mm | Burn wounds, tissue defects | Perouse Plastie |
| **Synthetic materials** | | | | |
| **Dermagraft** | Polyglactin mesh + allogeneic fibroblasts | 0.19 mm | Burn and chronic wounds, diabetic ulcers | Advanced BioHealing, LaJolla, CA, USA |
| **Polyactive** | Polyethylen oxide + polybutyliterephthalate | 0.25 mm | Bone, cartilage repair | Octoplus Inc. |

**Note:** None of the engineered skin substitutes containing living cells (even those approved in the US, like Apligraf®, Transcyte®, Dermagraf®, OrCell.) have been approved in Europe [Ruszczak (2003)].

* It is a bilayered cell therapy or composite skin substitute, not only a dermal substitute.