Skin Substitutes

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Abstract

The role of skin substitutes in burn surgery and in the treatment of chronic wounds is constantly evolving. New products are regularly being developed and approved for clinical use. Studies on existing products demonstrate their effectiveness in different clinical scenarios. However, cost-related concerns, inadequate physician education, and the drawbacks that still accompany every skin substitute have resulted in limited application of these modalities. Today, burn surgeons still rely mostly on old-fashioned skin grafts. Only a few burn centers in the world actually use some of these products in their routine treatment of wounds. This review provides an up-to-date overview of the latest developments in the field of skin substitutes. We examine the major commercially available skin substitute products and their performance, and briefly review the technologies and products that are under development but have not yet become widely available.

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Skin substitutes have a potentially important role in the treatment of burns and a wide variety of other wounds. This evolving modality provides the physician with a tool to rapidly cover or even close soft tissue deficits (wounds and burns) without the well-described liabilities of donor site morbidity, and in cases in which donor sites are unavailable.

Anatomically and functionally the skin has two layers. The epidermis, which is the superficial layer of the skin, provides a barrier against infection and moisture loss. The deep dermal layer is responsible for the elasticity and mechanical integrity of the skin. In wound management, there is an advantage to early coverage. Normally, ingrowths from wound edges close the wound, however in wounds more than a few centimeters wide the ingrowths from the wound edges are insufficient. In partial-thickness wounds, the deep dermis remains, and regeneration of the epidermis relies on residues of epidermal cells that lie deep in the dermal structures (skin appendages, i.e., hair follicles). It is important to mention that these ingrowths are all induced by different growth factors. In the case of full-thickness wounds, all epidermal and dermal structures are destroyed. Skin must be introduced in the form of a skin graft or flap. Another option to treat wounds is the application of a skin substitute. This family of products can be divided into three categories: the first type is grafts of cultured epidermal cells with no dermal components, the second type has only dermal components, and the third type is a bi-layer containing both dermal and epidermal elements.

Skin substitutes have several roles. Temporarily, they cover the wound thus preventing dehydration on the one hand, and keeping the wound bed moist (important for wound healing) on the other. In addition, some skin substitutes stimulate the host to produce a variety of cytokines and growth factors that promote wound healing.

Skin substitutes play a major role in burn care and are used for early burn coverage. Their use, especially in extensive burns, may increase survival and lead to a better recovery of function and appearance. Another important role for skin substitutes is in chronic wounds. In this review we address skin substitutes in two groups – wound closure and wound coverage. Wound closure requires a material to restore the epidermal barrier function and become incorporated into the healing wound, whereas materials used for wound coverage rely on the ingrowth of granulation tissue for adhesion. Materials for wound coverage are most suited for superficial burns, where they create an improved environment for epidermal regeneration by providing a barrier against infection and control water loss.

Skin substitutes may increase survival especially in extensive burns, and lead to a better recovery of function and appearance

Skin substitutes for wound coverage [Table 1]

Biobrane™

Bilaminate membrane [1]:

- Nylon mesh fabric: the nylon mesh is coated with peptides derived from porcine type I collagen, in order to aid adherence to the wound bed and fibrovascular ingrowth. Since nylon is not biodegradable this material cannot act as a dermal substitute
- Silicone: a thin semi-permeable layer.

Recommended uses:

- Donor sites
- Superficial partial-thickness burns. Applied within the first 6 hours after injury as it is best reserved for 'clean' wounds.

Table 1. Skin substitutes

Trade name	Layers	Cost	Cost per cm^2
Biobrane™ UDL, Rockford, IL, USA	1. Silicone 2. Nylon mesh 3. Collagen	5 x 5 cm NIS 100	NIS 4
Transcyte™ Smith & Nephew Inc., USA	1. Silicone 2. Nylon mesh 3. Collagen seeded with neonatal fibroblasts	13 x 9 cm NIS 7600	NIS 67
Apligraft™ Organogenesis Inc, MA, USA	1. Neonatal keratinocytes 2. Collagen seeded with neonatal fibroblasts	7.5 cm diameter disk NIS 5300	NIS 120
Dermagraft™ Smith & Nephew Inc., USA	1. Polyglycolic acid (Dexon™) or polyglactin-910 (Vycril™) seeded with neonatal fibroblasts	5 x 7.5 cm NIS 2300	NIS 60
Integra™ Integra Life Science Corp, Plainsboro, NJ, USA	1. Silicone 2. Collagen & glycosaminoglycan	10 x 25 cm NIS 6800	NIS 30
Alloderm™ LifeCell, NJ, USA	1. Acellular de-epithelialized cadaver dermis	4 x 12 cm NIS 2400	NIS 50
Epicel™ Genzyme Tissue Repair Corp, Cambridge, MA, USA	1. Cultured autologous keratinocytes		
Laserskin™ Fidia Advanced Biopolymers, Italy. Also marked as Vivoderm by ER Squibb & Sons Inc, Princeton, NJ, USA	1. Cultured autologous keratinocytes 2. Hyaluronic acid with laser perforations		
Cadaveric allograft Cryopreserved Lypophilized Glycerolized		Non-profit national skin bank	
Homograft		Operating room	

Costs are given in the standard supplied size and secondly per cm^2. Costs should be treated as a guide. NIS = new Israeli shekel; US$ 1 is 4.7 NIS.

When used in this manner on burn wounds, they are expected to heal within 10–14 days, thus reducing the time of inpatient treatment by 46% [2].

Biobrane has been used as temporary coverage for freshly excised full-thickness wounds. Adherence, fluid collection and subsequent autograft take are similar to results obtained with cryopreserved allograft, provided that bacterial counts are less than 105/g tissue [3].

Transcyte™ (formerly Dermagraft-TC)

In Transcyte, the collagen-coated nylon mesh used in Biobrane is seeded with neonatal fibroblasts [4,5]. As noted above, nylon is not biodegradable and therefore this material cannot act as a dermal substitute.

- Excised burn wounds: used as a temporary dermal analogue. When compared with cryopreserved allograft, Transcyte was easier to remove than allograft, resulting in less bleeding [6]. Histologically, the only significant difference was increased granulation tissue in the allograft-treated wounds [7]
- Partial-thickness burn wounds: usually require only conservative treatment. When partial-thickness wounds were treated with Transcyte they healed with less hypertrophic scarring compared to wounds treated with silver-sulfadiazine [8]. Transcyte was also shown to significantly improve the management and healing rate of partial-thickness facial burns, compared with standard open care [9].

Cultured allogeneic keratinocytes

The main use for allogeneic keratinocytes remains as a dressing in chronic open wounds, such as leg ulcers [5,10], or to speed the healing of donor sites [5,11]. In the clinical context there is no acute rejection, however allogeneic cells survive less than 1 week when grafted onto tattoo-excision wounds or ulcers [12]. This increases to more than 6 weeks when they are applied to a split-skin graft donor site [5]. The enhanced healing that follows the application of allogeneic keratinocytes is attributed to the secretion of growth factors and cytokines by the keratinocytes [5,13]. Cultured allogeneic keratinocytes are therefore regarded as materials for wound coverage, since they will not in themselves achieve wound closure.

Apligraf™ (Graftskin) – living skin equivalent, human skin equivalent

Apligraf is bi-layered. The deep layer combines living neonatal allogeneic fibroblasts in a gel of type I bovine collagen. The superficial layer consists of a cornified epidermal layer of neonatal allogeneic keratinocytes. This 'composite' skin substitute, consisting of two different cell types, is currently the most sophisticated commercially available tissue-engineered product, and thus the most expensive [4,5]. Its primary role is for the treatment of chronic ulcers [5,14]. It appears to hasten healing, particularly in deeper and more chronic wounds.

Dermagraft™

Dermagraft is a cryopreserved living dermal structure, manufactured by cultivating neonatal allogeneic fibroblasts on a polymer scaffold [15]. The fibroblasts become confluent within the polymer mesh, secreting growth factors and dermal matrix proteins (collagens, tenascin, vitronectin and glycosaminoglycans), thus creating a living dermal structure [16]. Dermagraft facilitates healing by stimulating the ingrowth of fibrovascular tissue from the wound bed as well as re-epithelization from the wound edges. It does not close the wound. Rather, it stimulates the healing of chronic lesions, such as diabetic foot ulcers [17,18].

Skin substitutes for wound closure

Alloderm

Alloderm is human cadaver skin from which the epidermis and dermal cellular components have been removed prior to cryopreserva-

tion [19]. Alloderm functions as a dermal graft but has little barrier function. Following application to a wound bed, it is repopulated by host cells, revascularized and incorporated into the tissue. It functions as a template for dermal regeneration. It is reported to have good 'take' rates and to reduce subsequent scarring of full-thickness wounds. Ultra-thin split-thickness skin grafts can be applied to Alloderm in a one-stage procedure. Thin split-thickness autografts with Alloderm were equivalent to thicker split-thickness autografts in final skin quality and cosmetic result [4].

Integra™

Integra is currently the most widely accepted synthetic skin substitute for use in burn patients [4,20,21]. Integra has a bi-laminar structure, consisting of cross-linked bovine collagen and glycosaminoglycan, and a silicone membrane on one side that provides epidermal barrier function. The silicone membrane is fenestrated with pores of 70–200 µm. Following application to a freshly excised wound, the collagen layer is bio-integrated in the wound to form a vascular 'neodermis', a process that takes approximately 3–6 weeks. Once this stage is reached, the silastic layer is removed and an ultra-thin split-thickness skin graft is applied. In a multicenter trial [22] the authors reported a subjective improvement in the cosmetic result of 149 cases in 106 patients. In particular, it was noted that donor site healing was shortened by 4 days and with less hypertrophic scarring. This is thought to be due to the thinness of the grafts that were harvested (0.15 mm compared to an average split-thickness skin graft that is 0.33 mm thick).

The use of Integra requires a two-stage procedure, with a minimum interval of 3 weeks between the application of the Integra and the split-skin grafting in order to allow neodermis formation.

Advantages:

- Improved elasticity and cosmetic result compared with an ultra-thin split-skin graft
- Reduced donor site morbidity (faster healing with less scarring) compared with a standard-thickness split-skin graft
- No risk of cross-infection
- Available off the shelf
- Does not necessitate a narrow window of time in which to perform the second stage.

Disadvantages:

- Relatively expensive when compared with cadaveric allograft skin from skin banks
- The learning curve is steep, with high failure rates initially.

Integra has an important role in providing immediate wound coverage following early excision in patients with insufficient donor sites. In addition, the ability to utilize thin grafts means that donor sites can be reharvested earlier.

Current research is focused on modifying the collagen-glycosaminoglycan matrix through the incorporation of peptides [23] and antibiotics [24]. Cultured autologous keratinocytes have also been shown to produce a surface epithelium when seeded as a suspension into Integra [25].

Cultured autologous keratinocytes

The clonal growth of keratinocytes has been possible for over 20 years [26]. Cultured keratinocyte sheets are available commercially from a number of commercial sources, as well as from suitably equipped university or hospital laboratories [4].

Disadvantages:

- Cost
- Requires skilled labor and quality control
- Long period of treatment: 3–5 weeks to produce 1.8 m^2 confluent sheets of cells from a 2 cm^2 biopsy
- A high degree of coordination is required between the burn unit and laboratory to use the cultured epithelial autograft sheets at their optimum
- The cultured autologous keratinocyte sheets are fragile. The resulting epithelium is unstable, giving rise to spontaneous blistering many months after grafting, increased susceptibility to infection, and contractures.

Pre-grafting the wound with allograft will encourage skin graft-take, as will the presence of a non-granulated dermal bed of allogeneic or autologous dermis [27].

Keratinocyte delivery systems

Systems for the delivery of cultured autologous keratinocytes have been developed in the hope that this may reduce costs and improve the take and quality of the resulting epidermis:

- Fibrin glue suspension: bonding cells together with fibrin glue. Complete healing was achieved within 14–21 days [28].
- Fibrin glue sheets: cultured keratinocytes have been grown on fibrin glue, and then transferred as a sheet.
- Upside-down membrane delivery systems (Laserskin™) [29]: a membrane delivery system created from a laser-perforated derivative of esterified hyaluronic acid. Keratinocytes are seeded *in vitro* onto the membrane and populate the laser-drilled pores.
- Sprayed cell suspensions [30]: sprayed cultured keratinocytes have been applied to wounds with autologous split-skin grafts meshed 3:1 in pigs. The cells were sprayed directly onto the wound without the use of fibrin glue. The wound is reported to heal faster and to be of superior quality where cells were sprayed.

Summary

Soft tissue injuries are not only disabling and disfiguring, but can also be life-threatening. A major problem encountered in extensive soft tissue trauma (as in major burns) is the scarcity of donor sites. This can significantly delay the final treatment. For years scientists have been looking for skin substitutes that can be used instead of autologus skin. An impressive array of skin

substitutes has been developed. These products serve plastic surgeons as important tools in their treatment of life-threatening major soft tissue trauma. What is even more interesting is the role that skin substitutes can play in the treatment of chronic wounds. Active skin substitutes have been developed that not only close the wound but also break the vicious cycle that created the chronic wound. However, cost-related concerns, inadequate physician education, and the drawbacks that every skin substitute still has, have resulted in limited application of these modalities. Today, burn surgeons still rely mostly on old-fashioned skin grafts. Few burn centers in the world actually use some of these products as routine wound treatment. In the future, as the cost of skin substitutes decreases and scientists develop a universal 'off-the-shelf' skin product, these products will certainly be widely used to treat soft tissue trauma and wounds.

A tool to rapidly cover or even close soft tissue deficits (wounds and burns) without the well-described liabilities of donor site morbidity

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