Science and Practicality of Tissue Products in Limb Salvage

23

Alexandra N. Verzella, Allyson R. Alfonso, and Ernest Chiu

Introduction

In 2017, the CDC estimated that the total direct and indirect expenditure on *diagnosed* diabetes in the USA was $327 billion, an increase of $56 billion dollars since 2012 [1]. Globally, the estimated cost in 2019 was 760 billion, and that is projected to reach 825 billion in 2030 [2]. The crude estimate of Americans with diabetes in 2018 was 34.1 million or 13.0%, and 7.3 million (21.4%) of whom were not aware of the diagnosis, with diabetic complications being the greatest contributor to healthcare expenditure in these patients [3, 4]. Some of these diabetes-related complications include kidney disease, ocular disease, death, and hospitalizations secondary to major cardiovascular disease, hyperglycemia, hypoglycemia, and diabetic ulcers. Foot ulcers develop in up to 34% of patients with diabetes, and failure of these ulcers to heal can lead to limb amputation [3, 4]. In fact, up to 5.6 out of 1000 adults with diabetes underwent a lower-extremity amputation for a total of 130,000 people in 2016 alone, underlining the importance of finding a way to better heal diabetic wounds and salvage limbs in these individuals [4].

Current Treatments

Diabetic wounds are precipitated by motor, sensory, and autonomic neuropathy. Motor deficits include atrophy of intrinsic muscles of the foot and dislocated metatarsophalangeal joints caused by unopposed power of the long flexors and extensors of the foot [5]. Sensory neuropathy decreases the protective ability to sense pain and impairs proprioception, causing balancing deficits. Autonomic system dysregulation then further contributes to the formation of diabetic foot ulcers through decreased sweat and oil gland secretions, which predisposes patients to cracks and fissures in the skin barrier [5].

According to guidelines from the American Diabetes Association, there are 6 vital components to the treatment algorithm for a diabetic wound which include: wound off-loading, surgical debridement of the wound early and often, maintenance of a moist wound bed, treatment of active infections, vascular assessment with correction of ischemia, and strict glycemic control [6–13]. Though there are a multitude of imperative components to healing a diabetic wound, the standard of care (SOC) for these wounds is limited to saline washes and vaseline gauze [14].

A. N. Verzella · A. R. Alfonso · E. Chiu (✉)
Hansjörg Wyss Department of Plastic Surgery, New York University Grossman School of Medicine, New York, NY, USA
e-mail: Alexandra.verzella@nyulangone.org; Allyson.alfonso@nyulangone.org; Ernest.chiu@nyulangone.org

C. E. Attinger, J. S. Steinberg (eds.), *Functional Limb Salvage*,
https://doi.org/10.1007/978-3-031-27725-2_23

In addition to the standard practices of care, the clinical practice guidelines published by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine also recommend negative pressure therapy, hyperbaric oxygen therapy, and biologics as adjunctive therapy for wounds recalcitrant to current SOC alone [15, 16]. However, before biologics like tissue products can be considered for use, the wound bed must be optimized through demonstrating adequate perfusion, debridement, and edema control.

Tissue Product Definition

In this chapter, tissue products are defined as anything that substitutes for skin and incorporates into the healing wound. The ideal tissue product for a diabetic foot ulcer should resist infection, prevent water loss, withstand the shearing forces endured by native skin, conform to irregular wound surfaces, lack significant antigenicity, and possess flexible thickness. It should also be cost-effective, widely available, easy to apply, durable and stable, and easy to store with a long shelf-life. Unfortunately, the ideal tissue product with all of these qualities does not currently exist.

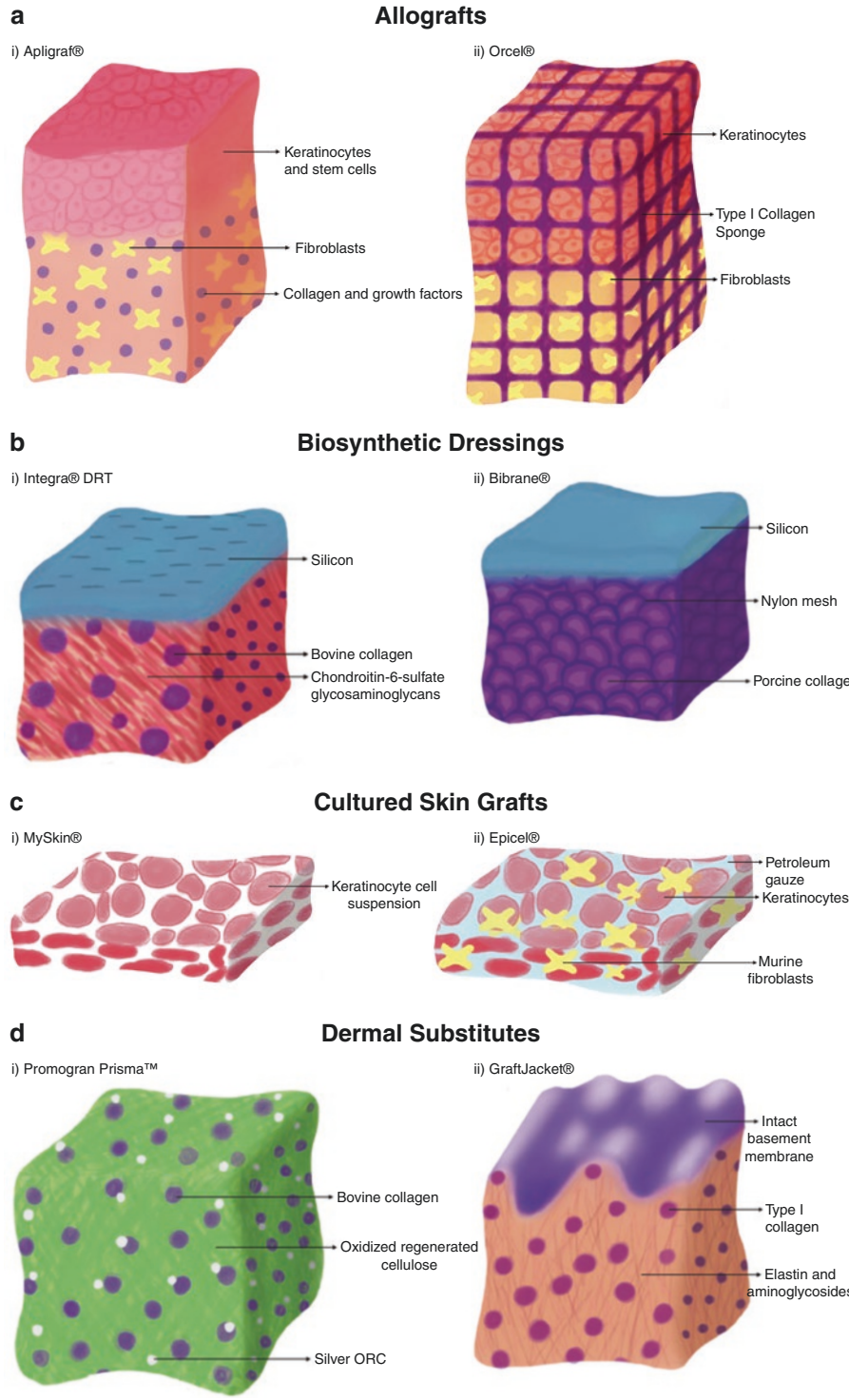
Several systems of classification for tissue products have been proposed such as Kumar's 3 classes that divide the products into temporary impervious dressing materials, single-layer durable substitutes, and composite skin substitutes or Dieckman et al.'s 2 classes of biomaterial or cellular products with allogenic, xenogenic, and autologous subcategories [17, 18]. Because there is a lack of consensus in these classification systems, in this chapter, biologic tissue products will be organized into their individual brand product and will be placed into 4 broader categories: (1) allografts/xenografts, (2) dermal substitutes, (3) biosynthetic dressings, and (4) cultured skin grafts. We will also highlight some of the currently commercially available products and do not endorse one over another.

Science and Practicality of Allografts and Xenografts

Allografts and xenografts are skin substitutes that are harvested from human and animal sources, respectively, that act as temporary skin grafts [19, 20].

Allografts can be either cellular or acellular and are exclusively derived from human sources, most commonly from neonatal foreskin. Cellular allografts contain living cells like fibroblasts and keratinocytes that encourage wound healing through secretion of growth factors and cytokines that promote the ingrowth of native host cells and neovascularization. Because these grafts retain non-autologous living cells, they can provoke an immunologic response in the host.

Apligraf® (Organogenesis, Inc., Canton, MA), previously called Graftskin, is a bilayer composite allograft that is indicated for full-thickness neuropathic diabetic foot ulcers that have been present for greater than 3 weeks and have not responded to SOC [21, 22] (Fig. 23.1a, Table 23.1). While Apligraf can be used in wounds that extend through the dermis, it is not indicated for diabetic ulcers that involve tendon, muscle, joint, or bone [22]. Its epidermal layer is comprised of living human neonatal foreskin-derived keratinocytes and stratum corneum, and its dermal layer contains bovine type I collagen and neonatal fibroblasts that produce growth factors and cytokines like VEGF, IL-6, and IL-8. These components function to activate host keratinocytes at the edge of the wound, regulate growth factors signals, provide a barrier against further wound damage and infection, control fibrosis and scar formation, and revitalize fibroblasts in the base of the wound—correcting ECM and matrix metalloproteinase balance. Because of the impact on fibrosis and scar formation, Apligraf also has reports of improved cosmesis and functional outcomes when used in chronic wounds [21, 23]. While Apligraf preserves many extracellular matrix (ECM) proteins and cytokines native to human skin, it does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels, or hair follicles [22]. In addition, Apligraf's allogenic cells are not able to survive long-term in



Adapted from Vig K, Chaudhari A, Tripathi S, et al. Advances in Skin Regeneration Using Tissue Engineering. *Int J Mol Sci.* 2017;18(4):789. Published 2017 Apr 7. doi:10.3390/ijms18040789

Fig. 23.1 Biologic skin substitutes. (**a**) Allografts: (i) Apligraf®, (ii) Orcel®. (**b**) Biosynthetic dressings: (i) Integra® DRT, (ii) Biobrane®. (**c**) Cultured skin grafts: (i) MySkin®, (ii) Epicel®. (**d**) Dermal substitutes: (i) Promogran Prisma™, (ii) GraftJacket®

Table 23.1 Biologic skin substitutes

	Manufacturer	Source	Intact cells	Application schedule	Shelf-life	Storage temperature	Difference over SOC	Indications
Allografts								
Apligraf®	Organogenesis, Inc., Canton, MA	Neonatal foreskin-derived keratinocytes with stratum corneum (epidermis) and bovine type-I collagen and neonatal fibroblasts (dermis)	Yes	Weekly	10 days	Room temperature	Yes	PMA[a] (1998)— Non-infected partial and full-thickness skin ulcers secondary to venous insufficiency >1 month resistant to standard therapies PMA (2001)—full-thickness neuropathic diabetic foot ulcers >3 weeks that have not responded to SOC [95] Off-label—epidermolysis bullosa [96], recurrent hernia repair, pressure sores, burn reconstruction [39]
Orcel®	Forticell Bioscience, Inc., NY, USA	Neonatal foreskin-derived epidermal keratinocytes and dermal fibroblasts cultured on bovine type-I collagen	Yes	One-time use	9 months	Room temperature	No	HDE[b] (2001)—burns (partial and full thickness) and recessive dystrophic epidermolysis bullosa with hand deformities PMA—fresh, clean, split-thickness, donor-site wounds in burn patients Off-label—chronic wounds (venous and diabetic ulcers) [20, 95]
Dermal substitutes								
GraftJacket®	Wright Medical Technologies, Inc., Memphis, TN	Cadaveric allogenic acellular dermis with an intact basement membrane and dermal matrix with ECM components	No	As needed	2 years	Room temperature	No	PHS 361—full-thickness diabetic foot ulcers that have been present for >1 week and extend through the dermis [95, 97] Off-label—superficial wounds, wounds with sinus tracts, and tendon and osteal repairs [98]
DermACELL®	LifeNet Health, Virginia Beach, VA	Decellularized cadaveric regenerative dermal matrix	No	As needed	1.5–4 years	Room temperature	No	PHS 361—chronic non-healing wounds (diabetic and venous ulcers), acute burns, breast reconstruction, and other soft tissue trauma and can be used on exposed joints, muscles, bones, and tendons [97]

	Manufacturer	Source	Intact cells	Application schedule	Shelf-life	Storage temperature	Difference over SOC	Indications
Amnioband®	MFT Biologics, Edison, NJ	Dehydrated human amnion and chorion allograft	Non-viable	Weekly	3 years	Room temperature	Yes	Partial and full-thickness neuropathic diabetic foot ulcers >6 weeks with no capsule, tendon, or bone exposure Internal and external tissue defects, including acute, chronic, and surgical wounds
Epifix®	MiMedx, Marietta, GA	Dehydrated human amnion and chorion membrane with epithelial cells, basement membrane, and avascular connective tissue	Non-viable	Minimal disruption is ideal but change as needed	5 years	Room temperature	Yes	Neuropathic ulcers, venous stasis ulcers, pressure ulcer, trauma wounds, and surgical wounds
Allopatch Pliable®	MFT Biologics, Edison, NJ	Acellular human reticular dermal tissue	No	Weekly	3 years	Room temperature	–	Partial and full-thickness neuropathic diabetic foot ulcers >6 weeks without exposed tendon or bone [97]
Epicord®	MiMedx, Marietta, GA	Dehydrated human umbilical cord allograft on an ECM of hyaluronic acid and collagen	Non-viable	As needed	5 years	Room temperature	Yes	Management of chronic and acute, including diabetic and other leg ulcers; burns treatment and tendon protection
Grafix®	Smith + Nephew Osiris Therapeutics, Inc., Columbia, MD	Cellular placental-based skin substitute	Yes	Weekly	3 years	−75 to −85 °C	No	"Wound cover" for management of chronic and acute wounds (diabetic foot ulcers, venous stasis ulcers, pressure ulcers), deep chronic wounds, tendon repair, burns [97]
AmnioExcel®	Integra Lifesciences, Plainsboro, NJ	Trilayered human allograft membrane (chorion–amnion–chorion)	Non-viable	Weekly	5 years	Room temperature	No	Management of complex chronic and acute wounds, including diabetic and venous/arterial ulcers, pressure ulcers, trauma wounds, surgical wounds, burns, and wounds with exposed muscle, tendon, bone and vital structures

(continued)

Table 23.1 (continued)

	Manufacturer	Source	Intact cells	Application schedule	Shelf-life	Storage temperature	Difference over SOC	Indications
Oasis®	Cook Biotech, Lafayette, IN	Acellular ECM from porcine jejunal submucosa	No	Weekly	2 years	Room temperature	No	510(k) (2006)—"management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds" [95]
Promogran Prisma®	3M, Saint Paul, MN	Collagen, oxidized regenerated cellulose, and silver on a sponge	No	Daily	Use by date printed on packaging	<25 °C	No	510(k)—"intended for the management of exuding wounds including: diabetic ulcers, venous ulcers, pressure ulcers, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, donor sites and other bleeding surface wounds, abrasions, traumatic wounds healing by secondary intention, dehisced surgical wounds" [95, 99]
Kerecis®	Kerecis, Arlington, VA	Decellularized Icelandic codfish skin that has been harvested, lyophilized, and freeze-dried	No	When previous Kerecis is absorbed and no longer visible	3 years	Room temperature	–	510(k) (2013)—"management of partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, surgical wounds, and draining wounds" [95, 100]

	Manufacturer	Source	Intact cells	Application schedule	Shelf-life	Storage temperature	Difference over SOC	Indications
Biosynthetic dressings								
Biobrane®	Smith and Nephew, St. Petersburg, FL	Porcine collagen in nylon mesh with semipermeable outer layer of silicone	No	Typically one time use	~3 years (see use by date on packaging)	Room temperature	–	510(k) (2009)—clean superficial burn wounds, donor sites after hemostasis, protective covering for meshed autografts [95] Off-label—dermabrasions, skin-graft harvesting, laser resurfacing, chronic wounds, venous ulcers [20, 101]
Transcyte®	Shire Regenerative Medicine, San Diego, CA	Neonatal foreskin fibroblasts seeded on bioabsorbable nylon mesh and covered with a layer of silicone	Yes	Typically one time use	18 months	−70 to −20 °C	–	PMA (1997)—temporary wound cover for surgically excised full-thickness and deep partial-thickness thermal burn wounds [21] Off-label—chronic legs ulcers, diabetic foot ulcers lasting >6 weeks, venous ulcers, pressure ulcers [21]
Integra®	Integra Lifesciences, Plainsboro, NJ	Bilayer of bovine collagen cross-linked with chondroitin-6-sulfate glycosaminoglycans with a semipermeable silicone outer layer	No	Minimal disruption is ideal but change as needed	6 months	Room temperature	Yes	510(k) (2002)—"management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, laceration, second-degree burns, skin tears), and draining wounds" [95]
Dermagraft®	Shire Regenerative Medicine, Inc., San Diego, CA	Cryopreserved neonatal foreskin fibroblasts cultured on a bioabsorbable polyglactin polymer mesh scaffold	Yes	Weekly	6 months	−75 °C +/- 10	Yes	PMA (2001)—"full-thickness diabetic foot ulcers >6 weeks' duration which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure" [20, 21, 39, 91] Off-label—chronic wounds, uninfected wounds, temporary or permanent covering prior to STSG graft on burn wounds [21, 75, 102]

(continued)

Table 23.1 (continued)

	Manufacturer	Source	Intact cells	Application schedule	Shelf-life	Storage temperature	Difference over SOC	Indications
Cultured skin grafts								
Hyalograft 3D®	Fidia Advanced Biopolymers, Abano Terme, Italy	Autologous fibroblasts seeded on a 3D hyaluronic matrix	Yes	One-time application	Several days	–	No	Non-infected chronic lower extremity ulcers (diabetic foot ulcers)
MySkin®	CellTrain Ltd., UK	Cell suspension of autologous sub-confluent keratinocytes	Yes	One-time application	2–3 days [103]	−90 °C	No	Burns and non-healing wounds
Laserskin®	Fidia Advanced Biopolymers, Abano Terme, Italy	Autologous sub-confluent keratinocytes and fibroblasts biopsy on a biodegradable benzyl esterified hyaluronic acid matrix	Yes	One-time application	2 days	–	No	510(k) (2001)—"management of wounds in the granulation phase such as pressure ulcers, venous and arterial ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process" [95]
Epicel®	Vericel Co., Cambridge, MA	Autologous keratinocytes and murine fibroblasts from epidermal biopsy seeded on petroleum gauze	Yes	One-time application	1 day	13–23 °C	–	HDE (2007)—deep dermal or full thickness burns comprising a total body surface area of at least 30% for use with split-thickness autografts or alone; post nevus excision [95] Off-label—diabetic and venous ulcers [21]
Kaloderm®	Tegoscience, Seoul, Korea	Allogenic keratinocytes from neonatal foreskin	Yes	One-time application	2 years	−60 °C	No	Non-infected diabetic foot ulcers and burns

[a]PMA-FDA premarket approval to evaluate the safety and effectiveness of products and devices that are integral in preventing serious illness or injury
[b]*HDE* humanitarian device exemption: regulatory pathway for products intended for use in rare/infrequent conditions

the host wound and are gradually replaced by native cells as the ulcer heals [21]. Small wounds are likely to only require one application, which increases the financial feasibility of using this product [21]. However, a disadvantage of Apligraf is that wounds require new applications once per week, decreasing its cost-effectiveness [21]. On average, Apligraf costs $86,226 per avoided amputation, and the direct costs associated with a lower-extremity amputation are roughly $50,000, a price that is considerably higher when the indirect costs of amputation are also considered [24, 25]. Another limitation of the allograft is its shelf-life of only 10 days at ambient temperatures [22]. It also requires debridement down to healthy bleeding tissue, but then, hemostasis must be achieved before application [22]. Use of Apligraf is contraindicated in infected wounds, patients allergic to bovine products (specifically bovine collagen), and individuals with a hypersensitivity to the agarose medium used for storage [22].

Orcel® (Forticell Bioscience, Inc., NY, USA), indicated in the treatment of chronic diabetic ulcers, is a composite allograft composed of a bilayered cellular matrix in which allogenic epidermal keratinocytes and dermal fibroblasts from neonatal foreskin are cultured in 2 distinct layers on a type I bovine collagen sponge [19, 27] (Fig. 23.1a, Table 23.1). As the wound heals, native host cells replace the allogenic keratinocytes and fibroblasts and fill in the collagen sponge scaffold [21, 25, 26]. Orcel has a shelf-life of 9 months, but it must be cryopreserved and is not indicated for use in infected wounds or in patients with allergies to penicillin, gentamycin, streptomycin, amphotericin B, or any animal products due to Orcel's processing [21, 27]. Additional allogenic tissue products are discussed in the dermal substitutes, biosynthetic dressings, and cultured skin graft sections.

While allografts are widely used and have many benefits, they can be limited by their availability, and xenografts can help to offset any shortage of allografts due to their constant supply [28]. Xenografts are made from acellular nonliving tissue that is derived from different species (most commonly bovine or porcine) and are composed of dermis in a variety of thicknesses or bilayered dermal–epidermal composites [29]. They must be acellular to avoid rejection and severe inflammation in the host, and because they are derived from non-human sources, they require increased processing to decrease their immunogenicity [6, 30]. However, there are a variety of different preparations for xenografts that can impact their contents and ultimate effect in patients [28]. Fresh, fresh frozen, lyophilized, and irradiated preparations all maintain the epidermal and dermal layers of the xenograft [28]. A more recent modification to xenograft processing includes the incorporation of aldehyde cross-linking and silver ions to amplify the antimicrobial properties of the graft, prolong its lifespan, decrease its antigenicity, and inhibit collagenase to prevent collagen breakdown [29–36]. Aldehyde cross-linking also removes the epidermis and the dermal appendages, resulting in an acellular dermal matrix that can be applied with either side down on the wound bed [28]. However, this cross-linking also can prolong inflammation and delay graft incorporation into the wound, effectively transforming the behavior of the graft from a biologic material into a more synthetic one [30].

Xenografts can be used as a temporary dressing before an autologous graft, and in partial thickness burns, xenograft matrices can be used as a permanent dressing [28]. Xenografts can be left in place until they naturally separate away from the healing skin of the underlying wound, but dressing changes should be done every 2–4 days in order to monitor the wound closely [28, 29]. However, given their immunogenicity, xenografts have increased potential for scarring and immunogenic rejection [37, 38]. Xenogeneic tissue products will be discussed in further detail in the dermal substitute and biosynthetic dressing sections.

Science and Practicality of Dermal Substitutes

Dermal substitutes are any tissue products that effectively act as dermis. They can be comprised of human or non-human-derived tissue that has then been processed to create an acellular scaf-

fold with a basement membrane and a complete extracellular matrix [17, 39]. Because of the complex nature of the dermal layer, dermal substitutes can be classified into cellular or acellular and living or nonliving [17, 39].

Acellular dermal matrix is composed of collagen, elastin, laminin, and glycosaminoglycans and derived from a decellularized cadaveric or xenogenic source. The tissue has no living cells remaining in the graft and therefore has the advantage of being immunologically inert, and revascularization begins within 1–2 weeks after implantation of the graft [5, 40]. They are better for use in fields that may be contaminated because they incorporate into a wound and achieve revascularization more rapidly, making them more resistant to any potential infection [40].

Graftjacket® (Wright Medical Technologies, Inc., Memphis, TN) is a cadaveric allogenic acellular dermal matrix which consists of an intact basement membrane and dermal matrix with ECM components, including type I collagen, elastin, and various aminoglycosides (Fig. 23.1d, Table 23.1). The dermal scaffold and intact basement membrane aid in adhering the tissue product to the wound and encourage ingrowth of cells and neovascularization through release of cytokines and growth factors [21, 41]. It is indicated for deep and superficial wounds, wounds with sinus tracts, and tendon and osteal repairs [21, 29, 41]. Because the product is allogenic and acellular, it can be used as a permanent skin substitute when autograft is not available in partial thickness wounds, but it can also be utilized for immediate reconstruction as a temporary dressing prior to autograft skin grafting [19, 21]. Graftjacket® helps to optimally prepare the wound prior to autograft placement by increasing wound bed vascularity and decreasing infection potential and fluid loss in the area [19]. Graftjacket® can also be applied concurrently with an autograft using the sandwich grafting technique in order to prevent wound desiccation and reduce bacterial colonization of the autograft [19]. The dermal substitute also comes premeshed for ease of clinical application and transudate drainage and has a shelf-life of 2 years at ambient temperatures [21, 41]. Graftjacket® should not be used in patients with autoimmune connective tissue disease or in infected wounds [41]. Moreover, because the tissue product is sourced from a human cadaver, there is always the potential for disease transmission despite extensive screening of donors [41].

DermACELL® (LifeNet Health, Virginia Beach, VA) is another example of an allogenic acellular dermal matrix that contains a nonliving dermal scaffold of matrikines, growth factors, cytokines, and extracellular matrix components such as collagen, elastin, and glycosaminoglycans [42–44] (Table 23.1). The intact structure acts a scaffold for host cells, and the signaling factors serve to promote cell ingrowth, proliferation, and angiogenesis [45]. The acellular dermal matrix (ADM) also contains fibroblast receptors that aid the cells in attaching to the scaffold, strengthening the matrix, and allowing it to withstand sheering forces comparable to those endured by healthy, intact dermis [42–44]. DermACELL® is indicated for diabetic foot ulcers and chronic non-healing wounds and can be used on exposed joints, muscles, bones, and tendons [30]. >97% of donor DNA is removed from the product during processing to mitigate disease transmission and minimize immunogenicity, and the product is then sterilized with radiation and low temperatures [42]. DermACELL® has a shelf-life of 1.5–4 years, depending on the exact product utilized, at room temperature [42]. However, DermACELL® is not to be used in patients with allergies to any of the antibiotics that are used in the processing and preparation of the product [42].

Placental membrane- and umbilical-derived products like Amnioband® (MFT Biologics, Edison, NJ) (ADM), Epifix® (MiMedx, Marietta, GA) (umbilical cellular dermal substitute) (ADM), Amniopatch Pliable® (cellular dermal substitute), Epicord® (umbilical cellular dermal substitute) (MiMedx, Marietta, GA), and Grafix® (Smith + Nephew Osiris Therapeutics, Inc., Columbia, MD) (cellular placental-derived skin substitute) can also act as dermal substitutes in chronic and diabetic wounds [46–48] (Table 23.1). These products can be preserved in a variety of different ways, including cryopreser-

vation in liquid nitrogen, silver nitrate, antibiotics, glycerol sheets, dried sheets, and gamma-irradiated sheets [49]. Umbilical and placental products decrease rates of infection and minimize loss of proteins, electrolytes, and fluids from wounds [19, 29]. The products are rich in growth factors, ECM proteins such as fibronectin and collagen, and cytokines that promote neovascularization, dermal fibroblast proliferation, and mesenchymal stem cell recruitment, allowing these products to perform dermal functions and closely mimicking the composition of human skin [49–51]. Placental and umbilical products undergo minimal processing to ensure that they maintain their inherent dermal scaffold, functional properties, and progenitor cells (in the case of the cellular products) [29]. These dermal substitutes are also able to conform to wounds with more complex anatomies [46–48, 51]. Grafix, specifically, can also be directly applied to exposed bone, tendons, and muscles [48]. While they are able to conform to complex anatomies, they are minimally adherent and have poor mechanical properties, necessitating more frequent dressing changes [29]. They also have a high biodegradability rate [51, 52]. Like other allogenic tissue products, there is always the risk of contamination and disease transmission despite donor screening [19, 29].

Oasis® (Cook Biotech, Lafayette, IN) is a xenogeneic non-cross-linked acellular dermal matrix (ADM) derived from processed porcine jejunum and indicated for use in diabetic ulcers and partial- and full-thickness wounds [53, 54] (Table 23.1). The processing required for this product is more extensive than that required for allogenic products because of the increased immunogenic potential of xenogeneic products. The processing removes cells from the porcine jejunum but leaves a scaffold of ECM components (glycosaminoglycans, fibronectin, proteoglycans, basic fibroblast growth factor, and transforming growth factor beta) intact [28, 53]. Because Oasis® lacks aldehyde cross-linking, it is less likely to cause scarring and inflammation, but is also does not possess the strength, prolonged lifespan, or decreased antigenicity that the cross-linking provides [30–36]. Dehydrated Oasis® can be stored for up to 2 years at room temperature and requires rehydration with normal saline once the product has been applied to the wound [29, 37]. However, because of its xenogeneic origin, no angiogenesis occurs, and the product does not take [28]. Therefore, it is only indicated for use as a temporary skin substitute and cannot be used permanently [29]. The product can remain on the wound until it sloughs off with the ingrowth of native epithelial cells to the wound [29]. However, many physicians prefer to change out the ADM every 2–4 weeks in order to more closely monitor the healing process because Oasis® is not a semi-transparent material [29]. Oasis® should not be used in patients with known porcine allergies, and patients from various religious backgrounds may be opposed to the use of a porcine product [21].

Like Oasis®, Promogran Prisma™ (3 M, Saint Paul, MN) is a xenogenic acellular dermal matrix, but instead of being derived from porcine components, it is composed of 55% bovine collagen, 44% oxidized regenerated cellulose, and 1% silver oxidized regenerated cellulose freeze-dried into a sponge [55, 56] (Fig. 23.1d, Table 23.1). Promogran™ works to heal wounds through minimizing protease activity, and, therefore, protecting growth factors from degradation [24]. The silver serves as an antimicrobial [promogran]. It is indicated for wounds that have been debrided of any necrotic tissue, including diabetic ulcers and trauma wounds [56]. Promogran Prisma™ should not be used in patients with known sensitivities or allergies to bovine products [56].

Kerecis® (Kerecis, Arlington, VA) is another example of a xenogeneic acellular dermal substitute. It is made from the skin of decellularized Icelandic codfish skin that has been harvested, lyophilized, and freeze-dried, and it is indicated for chronic vascular ulcers, trauma wounds, and partial- and full-thickness wounds, including diabetic ulcers [50, 57] (Table 23.1). The dermal substitute maintains its fat, protein, elastin, and glycans and has an abundant supply of antimicrobial agents such as omega-3 polyunsaturated fatty acid, eicosapentaenoic acid, and docosahexaenoic acid [50, 58]. Fish have dermis with

structures comparable to that of humans, but they also possess rich supplies of type I collagen and noninfectious microbiota that aid in the wound healing process [50, 59]. Through epidermal growth factors and fibroblast growth factors, the native collagen in the fish skin has the ability to promote collagen synthesis in the host's wound bed and stimulates fibroblast and keratinocyte migration, proliferation, and differentiation [50, 60]. Fish collagen is also able to be degraded and absorbed into the wound because of its high level of biocompatibility with human tissues [50, 60]. Kerecis® adheres well to the wound bed, which minimizes the number of applications necessary for wound healing [50]. Fish products also do not risk prion transmission like bovine and porcine derived skin substitutes. Kerecis® can easily be stored at ambient temperature for 3 years [50, 61, 62]. It also does not have the same restriction against placement on potentially infected wounds that many other skin substitutes possess, given its indication for use in trauma wounds. However, Kerecis® cannot be used in patients with fish sensitivities or allergies.

Science and Practicality of Biosynthetic Dressings

Biosynthetic dressings are acellular tissue products engineered to contain both biologic and nonbiologic non-degradable materials such as silicone, nylon, and polyglactin [19, 29, 63–65]. The dressings act as scaffolds to promote cell growth and generate neodermis [29]. A major advantage of biosynthetic dressings is that their compositions can be controlled and growth factors and cytokines can be added as needed. The biosynthetic outer layer acts as the epidermis, preventing loss of moisture and wound contamination. However, they are not able to mimic the architecture of the skin and do not have a basement membrane. Another disadvantage of these biosynthetic dressings is their ability to cause a robust inflammatory response in the tissue, causing significant scarring or even immune rejection of the product.

Biobrane® (Smith and Nephew, St. Petersburg, FL) is a bilaminar dressing with an inner layer of porcine collagen embedded in a nylon mesh covered by a semipermeable outer layer of silicon, which is indicated for use in the treatment of chronic wounds [5, 19, 21, 66] (Fig. 23.1b, Table 23.1). The layer of nylon mesh provides a scaffold for fibrovascular growth into the tissue product and wound, and the outer silicone-based layer serves as a microbial barrier and retains moisture. While Biobrane® is able to retain moisture, it is also sufficiently porous to allow for exudate drainage and antibiotic penetration to the wound when applied on top of the dressing [21]. Biobrane's structure and collagen binding work together to recruit fibrin and fibroblasts from the wound bed, helping the product securely adhere to the wound [28]. As the wound heals and the native skin regenerates and grows inward, the Biobrane® naturally separates away from the wound and can be trimmed away [21]. This process makes dressing changes painless [28]. The trimming process also decreases risk of infection as it prevents fluid accumulation, providing an outlet for drainage from the wound [28]. Because Biobrane® is not composed of human-derived allogeneic material, it does not pose the same risk of disease transmission as allogenic products. However, Biobrane® does have drawbacks of its own, including its immunogenicity and ability to cause scaring due to the synthetic materials [19]. Because of the antigenic potential of Biobrane®, it is not indicated for use as a permanent skin substitute and must be removed [19]. Its use is also limited to wounds without evidence of infection or eschar and wounds with an intact basement membrane and dermis because its architecture does not closely approximate that of normal skin and, therefore, cannot replace it effectively on its own [19].

Transcyte® (Shire Regenerative Medicine, San Diego, CA) is a biosynthetic dressing composed of allogeneic fibroblasts from neonatal foreskin that have been seeded onto a bioabsorbable nylon mesh scaffold covered with silicone, which is indicated for diabetic foot ulcers lasting more than 6 weeks [21] (Table 23.1). The fibroblasts are cultured ex vivo for 4–6 weeks on the scaffold, and when used on a diabetic wound, secrete ECM components and local growth factors [21,

67]. Transcyte® has a shelf-life of 1.5 years and is easier to remove than allografts, which is an important feature of a biosynthetic dressing given that they must be removed and cannot be used as permanent skin substitutes [21].

Integra® Dermal Regeneration Template (Integra Lifesciences, Plainsboro, NJ) is a bilayered matrix composed of bovine collagen cross-linked with chondroitin-6-sulfate glycosaminoglycans with a semipermeable silicone outer layer that acts as the epidermis (Fig. 23.1b). Integra® DRT is FDA approved for use in the healing of diabetic wounds [21] (Fig. 23.1b, Table 23.1). The porous matrix serves as a scaffold for autologous cell ingrowth, effectively regenerating a functional dermal layer [69]. Neovascularization of the dermal component of the membrane is expected to be completed at 3 weeks, and the top layer of silicone can be removed at 2–4 weeks in preparation for skin grafting, which happens roughly 3 weeks after the initial procedure in which Integra® DRT was placed [21, 68, 69]. Integra® DRT facilitates the migration of macrophages and fibroblasts into the wound and promotes the formation of granulation tissue, increasing the survival potential of both the wound and any graft that will be placed [21, 70]. Once the neodermis has formed in the healing wound, Integra's silicone layer can be removed, allowing for split-thickness skin graft placement on the neodermis [21, 70]. While Integra® can be used as an interim wound coverage until an autograft is ready, it can also act as an absorbable implant or a permanent skin substitute in full-thickness or deep partial thickness wounds [21]. However, for Integra® DRT to be used in wound healing, complete wound excision is required as it will not take on nonviable tissue and should not be applied on an infected wound [21, 69]. Because the tissue product is avascular, there is a high risk of infection and graft loss [21]. Integra® DRT should not be used in patients with hypersensitivities to bovine products or chondroitin [20]. Integra® DRT should ideally be placed on the same day as an excision or debridement because any delays can decrease the tissue products' ability to take.

Very similar to Integra® DRT, Integra® Bilayer Matrix (Integra Lifesciences, Plainsboro, NJ) is composed of a cross-linked bovine collagen-glycosaminoglycan biodegradable matrix and an outer layer of semipermeable polysiloxane (Figs. 23.1, 23.2, Table 23.1). The silicone helps to prevent water loss from the wound and improves durability of the tissue product [71]. The biodegradable matrix serves as a scaffold for neovascularization and cell ingrowth [71]. It indicated for partial- and full-thickness diabetic ulcers and wounds and is immediately available for wound coverage [29, 71]. Integra® Bilayer Matrix has also demonstrated better cosmesis and tissue elasticity than STSG alone [29]. Other advantages of Integra include a reduction in wound site morbidity, including reduced infection when compared to SOC alone [29]. This biosynthetic dermal substitute can be used in conjunction with negative-pressure wound therapy to decrease time to graft placement and increase take rates of skin grafts [29, 72]. While there are a multitude of advantages, Integra® also has a steep learning curve for use, and there is a significant risk of seroma or hematoma formation with Integra® (likely due to its use in acute wounds) [29]. However, surgeons can mitigate this risk by meshing the skin substitute prior to application to allow for improved wound drainage [29].

Dermagraft® (Shire Regenerative Medicine, Inc., San Diego, CA) is another example of a biosynthetic dressing, and it is composed of cryopreserved neonatal foreskin fibroblasts cultured on a bioabsorbable polyglactin polymer mesh scaffold [21, 29, 70] (Table 23.1). The allogenic fibroblasts then multiply and secrete growth factors such as collagen, tenascin, vitronectin, glycosaminoglycans, and other extracellular matrix proteins, encouraging granulation tissue production and migration of the patient's own cells into the wound bed [29, 73, 74]. The donor cells of the dressing are gradually replaced with fibrovascular tissue from the host over 3– 4 weeks [74]. Dermagraft® is indicated for full-thickness diabetic lower-extremity wounds that extend through the dermis but do not reach tendon, muscle, our bone and have been present for at least 6 weeks

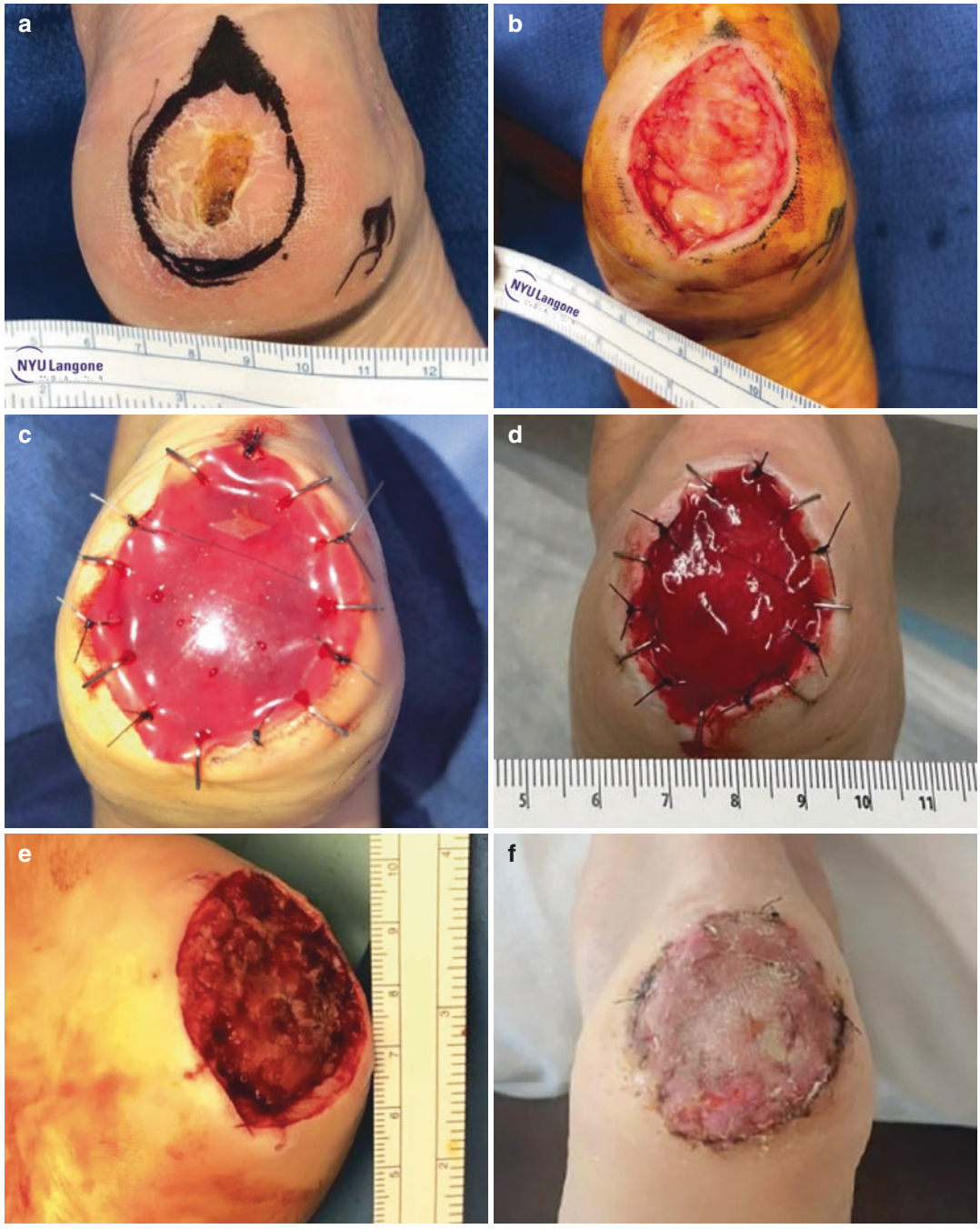


Fig. 23.2 Clinical images calcaneal foot view. (**a**) 54-year-old NIDDM with persistent chronic non-healing calcaneal wound for 3 years with normal pre-op vascular surgery evaluation and an HgA1c of 6.3. (**b**) A 2 cm wound/scar excision was performed to the calcaneal bone and (**c**) Integra® graft matrix was applied to accelerate healing over bone/tendon and increase heel pad thickness. (**d**) Negative-pressure wound therapy was utilized and (**e**) full-thickness skin graft was applied after 3 weeks. (**f**) Wound at 2 month follow-up visit

[21, 39]. The growth factors and cytokines are essential for building granulation tissue, stimulating matrix production, and angiogenesis. The polyglactin mesh has several advantages over collagen-based materials including improved strength and its ability to be broken down in vivo by hydrolysis [73]. The semi-transparency of Dermagraft® also allows for continuous wound surveillance during dressing changes [21]. Despite the xenogeneic and synthetic components of Dermagraft®, there has been very low incidence of rejection and infection [21, 75]. However, Dermagraft® is contraindicated in infected wounds, patients with bovine allergies, infected ulcer, ulcers with sinus tracts, and in wounds that have not yet been debrided [21]. Dermagraft® has a shelf-life of 6 months and is contraindicated in patients with bovine allergies, infected ulcers, and ulcers with sinus tracts [21]. Moreover, Dermagraft® is only used as a temporary coverage [21].

Science and Practicality of Cultured Skin Grafts

Cultured skin grafts are allogenic or autologous human keratinocytes or fibroblasts that have been expanded in culture onto a collagen matrix to produce a sheet suitable for grafting [76, 77]. The basal keratinocytes in cultured skin grafts are able to augment wound epithelialization [19]. However, there are significant disadvantages of using cultured skin grafts. They are fragile, and, therefore, difficult to manipulate during the application process and are challenging to handle while doing dressing changes [19]. Due to the fragility of the sheet, the take rate of cultured skin grafts can be difficult to predict and strict surgical immobilization is required to maximize adhesion. Additionally, cultured skin grafts cannot be applied to full-thickness wounds with exposed fat or fascia due to their inability to adhere to the wound without the anchoring fibrils and other dermal regenerative components located at the base of pilosebaceous layer of the dermis [19]. Another limitation of cultured skin grafts is their infection potential [19].

Hyalograft 3D® (Fidia Advanced Biopolymers, Abano Terme, Italy) is an example of a cultured skin graft that its derived from autologous fibroblast cells that have been seeded on a 3D hyaluronic acid matrix [78, 79] (Table 23.1). Similarly, Hyalomatrix® is composed of autologous fibroblasts on a hyaluronic acid base, but it covered by a silicon layer that helps to retain moisture, acting as a temporary epidermis [78]. Hyaluronic acid is one of the most common polysaccharides found in the native dermal extracellular matrix and acts to attract and proliferate fibroblasts and keratinocytes to the wound. These products, because they provide elements necessary for the formation of an ECM, are commonly used prior to split-thickness skin grafts [80]. In clinical practice, Hyalograft 3D® is commonly used in combination with Laserskin® for the treatment of diabetic foot ulcers [80]. However, the take rate of the product is unpredictable [19].

MySkin® (CellTrain Ltd., UK) is a cell suspension of sub-confluent autologous keratinocytes delivered on a polymer silicone scaffolds or as a spray (Fig. 23.1c, Table 23.1). The silicone substrate improves the grafts' ability to withstand the tearing and sheering forces that occur when manipulating cultured skin grafts. Additionally, the polymer substrate allows it to cover a larger wound than sub-confluent cells alone would have the potential to [81]. However, as of 2012, MySkin® was sold as a spray due to physician preference, simplifying the application process. In addition to ease of application, the use of a sprayed cell suspension has the added benefit of avoiding dispase, which is an enzyme that is necessary to release the epidermal sheets from the culture but also likely removes surface proteins on keratinocytes, decreasing the adhesive capacity of the cells [28]. As opposed to sheets of keratinocytes, the cell suspensions also contain melanocytes and papillary fibroblasts in variable ratios and quantities [28]. Use of a delivery substrate or spray and sub-confluent cells decreases the cell culture time necessary prior to application [28]. The time needed to culture a sufficient sub-confluent quantity of cells for use with diabetic foot ulcers is usually 15 days but can range between 11 and 19 days [28]. However, because

MySkin is cultured from autologous cells, preparation and culture time will always be required and will delay treatment of the wound, which is a significant disadvantage of MySkin and other autologous-based products.

Laserskin® (Fidia Advanced Biopolymers, Abano Terme, Italy) is composed of autologous sub-confluent keratinocytes and fibroblasts, tissue acquired from skin biopsy, that have then been cultured on a laser-microperforated biodegradable matrix of benzyl esterified hyaluronic acid, and it is indicated for diabetic foot ulcers [21, 29, 82, 83] (Table 23.1). The Laserskin® matrix allows for cell proliferation and migration into the wound, and the micro-perforations allows for drainage of wound exudate [21]. Like other autologous products, Laserskin has the advantage of negating any potential for rejection but also necessitates a premanufacture skin biopsy and culture time [21]. Because the cells are not confluent on the matrix, the time needed to culture is decreased in comparison to confluent cultured skin substitutes. The matrix of Laserskin lends to easier manipulation and handling during both initial application and dressing changes, and the transparency of the dressing allows for wound visualization and monitoring during dressing changes. Because the autologous cells are cultured on the scaffold that is then used as a part of the skin substitute, the use of the enzyme dispase is not required to remove keratinocyte sheets from culture flasks, mitigating disruption to keratinocyte surface proteins and adhesive potential of the cells [21]. Due to the preserved adhesive potential of the cells, Laserskin has good graft take and does not demonstrate the fragility that other cultured epithelial autografts possess. It has also demonstrated low rates of infection [21]. Laserskin® is limited by its availability in the USA, as it is currently only available for use in Europe [21]. Moreover, Laserskin® is also limited by its 2-day shelf-life [21].

Epicel® (Vericel Co., Cambridge, MA), indicated for use in diabetic foot ulcers, is a sheet of cultured skin substitute made from autologous keratinocytes with murine fibroblasts obtained from epidermal skin biopsy that is then placed on petroleum gauze [21, 84, 85] (Fig. 23.1c, Table 23.1). Epicel® is frequently used as an adjuvant therapy with an autologous split-thickness skin graft (STSG), but it can also be used when STSGs cannot be obtained due to the extent of an injury or wound (more likely in the setting of a burn, not a diabetic foot ulcer) [21]. Like other autologous grafts, the risk of rejection is mitigated. Epicel® can also permanently provide coverage of extensive wounds. However, Epicel® requires a premanufacture epidermal biopsy and about 3 weeks to culture a sufficient number of cells [21]. After 3 weeks of culturing, the graft has a shelf-life of only 1 day, complicating the application process [21, 86]. The take rate of Epicel can vary, and the long-term results of the product have shown variable efficacy [21]. The skin substitute also carries the risks of blistering, contractures, and infection [21].

Kaloderm® (Tegoscience, Seoul, Korea) is a cultured skin substitute composed of allogenic keratinocytes from the foreskin of a circumcised infant [87] (Table 23.1). Kaloderm® consists of an ECM, cytokine- and growth factor-secreting keratinocytes, and collagenases to encourage wound healing and decrease scar formation [87]. It is indicated for non-infected diabetic foot ulcers, and it can be stored for up to 24 months at -60 °C or 3 months at -15 °C [87]. After thawing for 10 min, Kaloderm can be directly applied to the wound, providing a skin substitute that can be used acutely without waiting for cells to propagate or culture [87].

Impact of Tissue Products for Diabetic Foot Wound Healing

Neuropathic foot ulcers are a significant complication of diabetes that can greatly increase health care costs due to wound care and the potential for hospitalizations and amputations.

Impact on Wound Healing

Tissue products do provide an advantage over SOC alone when measuring complete wound closure at 12 weeks [3, 88]. The mean number of

applications generally range from 1.2 to 10.1 [89]. Healing rates with tissue products at 12 weeks range from 24 to 100%, while healing rates with SOC alone ranged between 0 and 69% [88]. Diabetic ulcers treated with tissue products were 1.67 times more likely to demonstrate complete closure than ulcers treated with SOC alone [88, 90]. When the proportion of healed ulcers at 6 weeks is investigated, tissue products still demonstrate an advantage over SOC alone. The risk ratio for complete ulcer closure at 6 weeks is 2.81, favoring tissue products [88].

While all tissue products work to target various steps in the wound healing process, and, overall, they show an advantage over SOC for promoting complete wound closure, not all categories or brands of tissue products demonstrate an improvement in diabetic ulcer healing [88]. Among the tissue products, *dermal substitutes and biosynthetic dressings* were the two categories that demonstrated a statistically significant wound healing advantage over SOC [88, 89, 91]. The individual dermal substitutes that demonstrated significantly improved healing over SOC at 12 weeks were *Dermagraft and Apligraf/Graftskin*, but no difference was observed for Healaderm and Orcel [88]. The biosynthetic dressings with significant advantages over SOC were *Amnioband, Amniopatch Pliable, Epicord, and Epifix*, while Grafix, Graftjacket, Promogram, and Oasis showed no advantage over SOC [88]. In contrast to dermal substitutes and biosynthetic dressings, cultured skin grafts (as an overall tissue product category) showed no significant difference over SOC, as was the case with the individual cultured skin grafts that were studied (Hyalograft, Kaloderm, and MySkin) [88, 89]. Of the individual products studied when examining closure of ulcers at 6 weeks, *Amnioband, Allopatch Pliable, and Integra* showed significant advantages over SOC alone, but Amnioexcel did not [88]. Other individual tissue products may also show a significant advantage in diabetic wound healing over SOC, but there are currently insufficient studies for some individual brands to draw a significant conclusion.

Both dermal substitutes and biosynthetic dressings demonstrated improvement over SOC alone, but when compared against each other, the studies do not definitely demonstrate superiority of one product over the other [88, 92, 93]. In order to definitively determine a gold standard of skin substitutes, more prospective comparative trials are required to allow providers to make evidence-based decisions on which skin substitute to use in their practice [88].

Overall, tissue products show a modest decrease in healing time of diabetic ulcers when compared to standard care alone, and dermal substitutes demonstrate the most significant effects over SOC. However, given the varying evidence for these tissue products, at this time, it is difficult to draw a definitive conclusion about which product to use, and therefore, tissue product choice remains individual physician preference dependent.

Determining and comparing time to complete healing has remained a challenge in the field due to heterogeneity of data collection and reporting [88]. However, the majority of studies do favor use of skin substitutes for wound healing [88].

Impact on Limb Salvage

There is a small absolute risk reduction for amputation when comparing SOC and tissue products [90]. In patients with lower-extremity diabetic ulcers, there was a significant reduction in the number of minor amputations in the tissue product group, with a 3.9% rate of amputation in the advanced treatment group compared to the 4.3% rate of amputation in the standard of care group [3]. The difference in major amputations between the two groups was more significant with a 50% decrease in major amputations in the advanced treatment tissue product group when compared to SOC alone with amputation rates of 1.6% and 3.2%, respectively [90]. Despite some evidence of minimally decreasing rates of amputation, the data is insufficient to draw definitive conclusions about the efficacy of tissue products in preventing amputations [3].

In addition to modest decreases in amputation rates, other practical aspects of tissue product implementation in diabetic wound healing

include lower readmission rates (6.4% vs. 4.0%) and fewer ED visits (23.1% vs. 18.3%) [3]. There is also no significant increase in length of hospital stay for patients treated with tissue products over the length of hospital stay for patients treated with SOC alone [3].

Financial Comparison

While there are an abundance of studies that focus on the wound healing abilities of various tissue products, only recently there has been an increase in studies researching the cost-effectiveness of these tissue products to determine if there is an economic incentive for our healthcare system and patients. While tissue product treatments may cost an average of an additional $1058 over SOC alone, this increase is offset by their ultimate long-term impact on wound healing through decreased minor and major lower-extremity amputations, increased ulcer-free weeks, and fewer ED visits and hospital readmissions [90, 94]. Amputations themselves can cost up to 10–40x the amount that would be required to treat diabetic foot wounds before they necessitate an amputation [94]. Tissue products can also provide a modest impact on quality adjusted life years (QALYs), providing an increase of 0.022 QALYs and 6.69 ulcer-free weeks over SOC alone [94]. Additionally, tissue products provided an incremental cost-effectiveness ratio of $48,242 per QALY when compared with SOC alone [94].

All tissue products examined demonstrate decreased cost-effectiveness in the hospital outpatient setting when compared to treatment in a physician's office due to higher application costs [89] (Table 23.2). A single diabetic foot wound, when treated with tissue products in the hospital outpatient setting cost an average of $2001–$14,507, whereas the average cost of treatment in an office ranged between $1207 and $8791 [89]. The allogenic dermal matrices GraftJacket, Integra DRT, and Dermagraft are capable of healing more ulcers for $1000 per patient than the other products studied by Samsell et al., demonstrating the highest level of cost-efficiency of the skin substitutes investigated [89].

In order to evaluate whether tissue products are an economically sustainable option for diabetic ulcers, the cost of the skin substitutes, as well as the long-term impact of wound closure, limb salvage, and patient satisfaction with limb function should be taken into consideration. In addition, the cost that patients will need to pay out-of-pocket should also be taken into consideration when determining treatment method and tissue product selection (Table 23.3).

Table 23.2 Parameters utilized to determine incurred costs of various tissue products to heal a single DFU

Tissue product	Mean number of applications	Product cost per application on 5cm^2 wound	Jan 2018 CMS ASP cost/cm^2	Cost of product per treated wound
ApliGraf	2.5	$1,359.34	$30.89	$3,398.34
DermACELL	1.2	$1,060.96	$66.31	$1,273.15
Dermagraft	6.3	$1,241.63	$33.11	$7,822.24
EpiFix	3.5	$990.08	$165.01	$3,465.27
Grafix	8.7	$805.70	$134.28	$7,009.62
GraftJacket	1.3	$774.74	$96.84	$1,007.17
Integra DRT	2.0	$901.01	$128.72	$1,802.02
Oasis ultra	10.1	$115.58	$11.01	$1,167.40

CMS centers for medicare and medicaid services, *ASP* average selling price

Table 23.3 Costs of treating DFUs in hospital outpatient departments and physicians' offices and estimated costs to patients for various biologic skin substitutes

Tissue product	Cost of treating one DFU in physician's office	Estimated patient cost in physician's office	Bundled HOPD payment	Cost of treating one DFU in HOPD	Estimated patient cost in HOPD
ApliGraf	$3,781.74	$756	$3,921.08	$4,168.58	$834
DermACELL	$1,457.18	$291	$1,882.12	$2,000.92	$400
Dermagraft	$8,791.41	$1,758	$9,022.90	$9,648.54	$1,930
EpiFix	$4,002.03	$800	$5,489.51	$5,836.01	$1,167
Grafix	$8,343.85	$1,669	$13,645.34	$14,506.64	$2,901
GraftJacket	$1,206.54	$241	$2,038.96	$2,167.66	$434
Integra DRT	$2,108.74	$422	$3,136.86	$3,334.86	$667
Oasis Ultra	$2,716.33	$543	$4930.82	$5,930.72	$1,186

HOPD hospital outpatient department

Conclusion

The shear magnitude of tissue products on the market, with new skin substitutes continually being developed, complicates the synthesis and analysis of these products. The information in this chapter only scratches the surface of tissue products available for diabetic wound healing, attempting to highlight the tissue products that are most commonly used. Some tissue products were able to show an improvement in wound closure over SOC, while others made no significant impact on healing time. However, tissue products overall did show a very modest benefit in limb salvage, decreasing rates of both minor and major lower-extremity amputations.

Not only do allogenic dermal matrices demonstrate a greater ability to heal diabetic ulcers than their other tissue product counterparts, but they also exhibit the greatest cost-efficiency of the tissue products examined in this study [3, 89]. However, the absence of standardized metrics in diabetic foot wound literature poses a considerable problem with drawing conclusions and comparing study results. There is no standardization of the categorization of skin substitutes, with various studies putting the same tissue product in different categories, confusing the results and diminishing comparability of studies. Inconsistency in reported healing endpoints and study timelines in concert with new tissue products rapidly being released on the market also complicate study comparison. Twelve weeks was traditionally the endpoint used in studying diabetic wound healing, whereas now studies have started to use 16 weeks, which may be a more appropriate endpoint for wound closure. Additionally, more studies are needed to determine the long-term impact of tissue products on these chronic wounds.

While this chapter works to investigate the impact of skin substitutes on healing diabetic foot ulcers, we are not able to draw definitive conclusions on the long-term effects of these products or post-closure adverse events. Future studies should continue to focus on the potential of tissue products in diabetic wound closure to better understand the long-term implications of using these products. There is also a relative paucity of research on the impact of tissue products on amputation rates and limb salvage, an important endpoint to measure long-term impacts of tissue product efficacy.

As we move toward further evidence-based medicine and efficiency, it is important that we choose a product that will continue to evolve and be mindful of the cost as we move to bundle payment and cost-efficiency.

Acknowledgments No acknowledgments are made.

References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care. 2018;41(5):917–28. [cited 2021 Jul 24]: 11p. https://diabetesjournals.org/care/article/41/5/917/36518/Economic-Costs-of-Diabetes-in-the-U-S-in-2017.
2. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: results from the International diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract. 2020;162:108072.
3. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med. 2017;376(24):2367–75.
4. Centers for Disease Control and Prevention. National diabetes statistics report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2020. [cited 2021 Oct 16]. https://www.cdc.gov/diabetes/data/statistics-report/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdiabetes%2Fdata%2Fstatistics%2Fstatistics-report.html.
5. Reddy G. Foot ulcers. In: Janis JE, editor. Essentials of plastic surgery. 2nd ed. Boca Raton, FL: CRC Press/Quality Medical Publishing, Inc.; 2014. p. 667–81.
6. Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and management of diabetic foot complications. Arlington, VA: American Diabetes Association; 2018. https://doi.org/10.2337/db20182-1. [cited 2021 Jan 8]. 20p. https://www.ncbi.nlm.nih.gov/books/NBK538977/pdf/Bookshelf_NBK538977.pdf.
7. Boulton AJM, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Sue Kirkman M, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care. 2008;31(8):1679–85.
8. Aldana PC, Khachemoune A. Diabetic foot ulcers: appraising standard of care and reviewing new trends in management. Am J Clin Dermatol. 2020;21(2):255–64.
9. Lavery LA, Davis KE, Berriman SJ, Braun L, Nichols A, Kim PJ, et al. WHS guidelines update: diabetic foot ulcer treatment guidelines. Wound Repair Regen. 2016;24(1):112–26, 112.
10. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018;1411(1):153–65.
11. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious diseases society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):e132–e73. https://doi.org/10.1093/cid/cis346. [cited 2021 Nov 6]. https://academic.oup.com/cid/article/54/12/e132/455959.
12. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ, International Working Group on the Diabetic Foot. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev. 2016;32(Suppl 1):2–6.
13. Vatankhah N, Jahangiri Y, Landry GJ, Moneta GL, Azarbal AF. Effect of systemic insulin treatment on diabetic wound healing. Wound Repair Regen. 2017;25(2):288–91.
14. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care. 1999;22(5):692–5.
15. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the society for vascular surgery in collaboration with the American podiatric medical association and the society for Vascular Medicine. J Vasc Surg. 2016;63(2 Suppl):S3–21.
16. Janis JE, Harrison B. General management of complex wounds. In: Janis JE, editor. Essentials of plastic surgery. 2nd ed. Boca Raton, FL: CRC Press/Quality Medical Publishing, Inc; 2014. p. 10–6.
17. Kumar P. Classification of skin substitutes. Burns. 2008;34(1):148–9.
18. Dieckmann C, Renner R, Milkova L, Simon JC. Regenerative medicine in dermatology: biomaterials, tissue engineering, stem cells, gene transfer and beyond. Exp Dermatol. 2010;19(8):697–706.
19. Halim AS, Khoo TL, Mohd Yussof SJ. Biologic and synthetic skin substitutes: an overview. Indian J Plast Surg. 2010;43(Suppl):S23–8.
20. Gupta S, Mohapatra DP, Chittoria RK, et al. Human skin allograft: is it a viable option in management of burn patients? J Cutan Aesthet Surg. 2019;12(2):132–5, 132.
21. Vyas KS, Vasconez HC. Wound healing: biologics, skin substitutes, biomembranes and scaffolds. Healthcare (Basel). 2014;2(3):356–400.
22. Apligraf®. Package insert. Canton, MA: Organogenesis Inc.; 2016.
23. Waymack P, Duff RG, Sabolinski M. The effect of a tissue engineered bilayered living skin analog, over meshed split-thickness autografts on the healing of excised burn wounds. The Apligraf burn study group. Burns. 2000;26(7):609–19.
24. Chow I, Lemos EV, Einarson TR. Management and prevention of diabetic foot ulcers and infections: a health economic review. Pharmacoeconomics. 2008;26(12):1019–35.
25. Ulbrecht JS, Cavanagh PR, Caputo GM. Foot problems in diabetes: an overview. Clin Infect Dis. 2004;39(Suppl 2):S73–82.
26. Kanokpanont S, Damrongsakkul S, Ratanavaraporn J, Aramwit P. An innovative bi-layered wound dress-

ing made of silk and gelatin for accelerated wound healing. Int J Pharm. 2012;436(1–2):141–53.
27. Orcel™. (Bilayered cellular matrix) instructions for use for managing donor sites in burn patients. New York, NY: Ortec International, Inc.; 2001. Orcel; [cited 2021 Dec 3]; 12p. https://www.accessdata.fda.gov/cdrh_docs/pdf/P010016c.pdf.
28. Sharma KS, Ralston D, Giblin V, MacNeil S. Engineering of accepted skin-equivalent tissue for tissue repair: current state and perspectives. In: Reis IL, editor. Encyclopedia of Tissue engineering and regenerative medicine. 1st ed. San Diego, CA: Academic Press, Inc.; 2019. p. 285–98.
29. Shores JT, Gabriel A, Gupta S. Skin substitutes and alternatives: a review. Adv Skin Wound Care. 2007;20(9 Pt 1):493–510.
30. Wan D, Potter J. Biomaterials. In: Janis JE, editor. Essentials of plastic surgery. 2nd ed. Boca Raton, FL: CRC Press/Quality Medical Publishing, Inc.; 2014. p. 87–106.
31. Turza KC, Butler CE. Adhesions and meshes: synthetic versus bioprosthetic. Plast Reconstr Surg. 2012;130(5 Suppl 2):206S–13S.
32. Patel KM, Bhanot P. Complications of acellular dermal matrices in abdominal wall reconstruction. Plast Reconstr Surg. 2012;130(5 Suppl 2):216S–24S.
33. Dunn RM. Cross-linking in biomaterials: a primer for clinicians. Plast Reconstr Surg. 2012;130(5 Suppl 2):18S–26S.
34. Novitsky YW, Rosen MJ. The biology of biologics: basic science and clinical concepts. Plast Reconstr Surg. 2012;130(5 Suppl 2):9S–17S.
35. Bengtson B. Discussion: use of dermal matrix to prevent capsular contracture in aesthetic breast surgery. Plast Reconstr Surg. 2012;130(5 Suppl 2):137S–41S.
36. Butler CE, Burns NK, Campbell KT, Mathur AB, Jaffari MV, Rios CN. Comparison of cross-linked and non-cross-linked porcine acellular dermal matrices for ventral hernia repair. J Am Coll Surg. 2010;211(3):368–76.
37. Liu Y, Panayi AC, Bayer LR, Orgill DP. Current available cellular and tissue-based products for treatment of skin defects. Adv Skin Wound Care. 2019;32(1):19–25.
38. Catalano E, Cochis A, Varoni E, Rimondini L, Azzimonti B. Tissue-engineered skin substitutes: an overview. J Artif Organs. 2013;16(4):397–403.
39. van der Veen VC, van der Wal MB, van Leeuwen MC, Ulrich MM, Middelkoop E. Biological background of dermal substitutes. Burns. 2010;36(3):305–21.
40. Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review. Plast Reconstr Surg. 2012;130(5 Suppl 2):27S–34S.
41. Graftjacket®. Regenerative tissue matrix instructions for use [package insert]. Memphis, TN: Wright Medical Technology; 2015.
42. Dermacell AWM. Instructions for use [package insert]. Virginia Beach, VA: LifeNet Health; 2019.
43. Dermacell AWM®. Human acellular dermal matrix (hADM). Virginia Beach, VA: LifeNet Health; 2020. [cited 2021 Dec 19]. https://www.lifenethealth.org/sites/default/files/files/68-65-040-01.pdf.
44. Dermacell AWM®. Technical overview. Virginia Beach, VA: LifeNet Health; 2019. [cited 2021 Dec 19]. https://www.lifenethealth.org/sites/default/files/files/DermACELL%20AWM%20Technical%20Overview(1).pdf.
45. Capito AE, Tholpady SS, Agrawal H, Drake DB, Katz AJ. Evaluation of host tissue integration, revascularization, and cellular infiltration within various dermal substrates. Ann Plast Surg. 2012;68(5):495–500.
46. MFT allograft tissue instructions for use [package insert]. Edison, NJ: Musculoskeletal Transplant Foundation; 2016.
47. Epifix dehydrated human amnion/chorion membrane allograft information/instructions for use [package insert]. Marietta, GA: MiMedx Tissue Services, LLC; 2017.
48. Grafix®. Cryopreserved placental membrane [package insert]. Columbia, MD: Smith + Nephew; 2021.
49. Bujang-Safawi E, Halim AS, Khoo TL, Dorai AA. Dried irradiated human amniotic membrane as a biological dressing for facial burns: a 7-year case series. Burns. 2010;36(6):876–82.
50. Bay C, Chizmar Z, Reece EM, Yu JZ, Winocour J, Vorstenbosch J, et al. Comparison of skin substitutes for acute and chronic wound management. Semin Plast Surg. 2021;35(3):171–80.
51. DiDomenico LA, Orgill DP, Galiano RD, Serena TE, Carter MJ, Kaufman JP, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. Plast Reconstr Surg Glob Open. 2016;4(10):e1095. https://doi.org/10.1097/GOX.0000000000001095. [cited 2021 May 11]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5096542/pdf/gox-4-e1095.pdf.
52. Farhadihosseinabadi B, Farahani M, Tayebi T, et al. Amniotic membrane and its epithelial and mesenchymal stem cells as an appropriate source for skin tissue engineering and regenerative medicine. Artif Cells Nanomed Biotechnol. 2018;46(sup2):431–40.
53. Hodde JP, Ernst DM, Hiles MC. An investigation of the long-term bioactivity of endogenous growth factor in OASIS wound matrix. J Wound Care. 2005;14(1):23–5.
54. OASIS®. Matrix product guide. Fort Worth, TX: Smith + Nephew Inc.; 2019. [cited 2021 Dec 17]. https://www.smith-nephew.com/documents/education%20and%20evidence/literature/2020/awm/us%20customer%20support%20collections/bio%20tissue%20products/oasis%20portfolio%20product%20guide.pdf.
55. Cullen B, Smith R, McCulloch E, Silcock D, Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic

foot ulcers. Wound Repair Regen. 2002;10(1):16–25, 16.
56. Promogran Prisma™. Wound balancing matrix indications and applications. St. Paul, MN: 3M; 2020. [cited 2021 Dec 15]. https://www.acelity.com/healthcare-professionals/global-product-catalog/catalog/promogran-prisma-wound-balancing-matrix.
57. Kerecis. Omega3 wound instructions for use. Isafjordur: Kerecis Limited; 2020.
58. Alam K, Jeffery SLA. Acellular fish skin grafts for management of split thickness donor sites and partial thickness burns: a case series. Mil Med. 2019;184(Suppl 1):16–20, 16.
59. Lima-Junior EM, de Moraes Filho MO, Costa BA, Fechine FV, de Moraes ME, Silva-Junior FR, et al. Innovative treatment using tilapia skin as a xenograft for partial thickness burns after a gunpowder explosion. J Surg Case Rep. 2019;2019(6):1–4. [cited 2021 Apr 22]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6565829/pdf/rjz181.pdf doi:10.1093/jscr/rjz181.
60. Chen J, Gao K, Liu S, Wang S, Elango J, Bao B, et al. Fish collagen surgical compress repairing characteristics on wound healing process in vivo. Mar Drugs. 2019;17(1):1–12. https://doi.org/10.3390/md17010033. [cited 2021 Mar 17]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6357035/pdf/marinedrugs-17-00033.pdf.
61. Kerecis. Kerecis intact fish-skin technology. Isafjordur: Kerecis; 2010. [updated 2021; cited 2021 Dec 17]. https://www.kerecis.com/omega3-fishskin.
62. Kerecis. Fish-skin graft rich in omega3 fatty acids. Iceland: Kerecis; 2010. [updated 2021; cited 2021 Dec 17]. https://www.kerecis.com/omega3-wound.
63. Cassidy C, St Peter SD, Lacey S, Beery M, Ward-Smith P, Sharp RJ, et al. Biobrane versus duoderm for the treatment of intermediate thickness burns in children: a prospective, randomized trial. Burns. 2005;31(7):890–3.
64. Demling RH. Burns. N Engl J Med. 1985;313(22):1389–98.
65. Ferreira M, Paggiaro A, Isaac C, Neto N, Santos G. Skin substitutes: current concepts and a new classification system. Rev Bras Cir Plást. 2011;26(4):696–702.
66. Smith + Nephew. Biobrane. Fort Worth, TX: Smith + Nephew Inc.; 2021. [cited 2021 Dec 26]. https://www.smith-nephew.com/key-products/advanced-wound-management/other-wound-care-products/biobrane.
67. Bello YM, Falabella AF, Eaglstein WH. Tissue-engineered skin. Current status in wound healing. Am J Clin Dermatol. 2001;2(5):305–13.
68. Arteche Pujana M, Pérez-Álvarez L, Cesteros Iturbe LC, Katime I. Biodegradable chitosan nanogels crosslinked with genipin. Carbohydr Polym. 2013;94(2):836–42.
69. Integra®. Dermal regeneration template Integra® Meshed dermal regeneration template [package insert]. Princeton, NJ: Integra LifeSciences Co.; 2020.
70. Hansen SL, Voigt DW, Wiebelhaus P, Paul CN. Using skin replacement products to treat burns and wounds. Adv Skin Wound Care. 2001;14(1):37–46, 37.
71. Integra®. Meshed bilayer wound matrix instructions for use [package insert]. Plainsboro, NJ: Integra LifeSciences Co.; 2013.
72. Jeschke MG, Rose C, Angele P, Füchtmeier B, Nerlich MN, Bolder U. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. Plast Reconstr Surg. 2004;113(2):525–30.
73. Organogenesis. Dermagraft human fibroblast-derived dermal substitute directions for use. La Jolla, CA: Organogenesis Inc.; 2015. [cited 2021 Nov 18]. https://dermagraft.com/pdf/Dermagraft-Directions-for-Use.pdf.
74. Mansbridge J, Liu K, Patch R, Symons K, Pinney E. Three-dimensional fibroblast culture implant for the treatment of diabetic foot ulcers: metabolic activity and therapeutic range. Tissue Eng. 1998;4(4):403–14.
75. Hansbrough JF, Mozingo DW, Kealey GP, Davis M, Gidner A, Gentzkow GD. Clinical trials of a biosynthetic temporary skin replacement, Dermagraft-transitional covering, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. J Burn Care Rehabil. 1997;18(1 Pt 1):43–51, 18, 43.
76. Greenwood JE. Hybrid biomaterials for skin tissue engineering. In: Albanna MZ, Holmes IV JH, editors. Skin Tissue engineering and regenerative medicine. 1st ed. San Diego, CA: Academic Press, Inc.; 2016. p. 185–210.
77. Eisenberg M, Llewelyn D. Surgical management of hands in children with recessive dystrophic epidermolysis bullosa: use of allogeneic composite cultured skin grafts. Br J Plast Surg. 1998;51(8):608–13.
78. Vig K, Chaudhari A, Tripathi S, Dixit S, Saho R, Pillai S, et al. Advances in skin regeneration using tissue engineering. Int J Mol Sci. 2017;18(4):1–19. https://doi.org/10.3390/ijms18040789. [cited 2021 Jun 7]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412373/pdf/ijms-18-00789.pdf.
79. Límová M. Active wound coverings: bioengineered skin and dermal substitutes. Surg Clin North Am. 2010;90(6):1237–55.
80. Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. J R Soc Interface. 2010;7(43):229–58.
81. Savoji H, Godau B, Hassani MS, Akbari M. Skin tissue substitutes and biomaterial risk assessment and testing. Front Bioeng Biotechnol. 2018;6(86):1–18. https://doi.org/10.3389/fbioe.2018.00086. [cited

2021 Apr 5]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6070628/pdf/fbioe-06-00086.pdf.
82. Ramos-e-Silva M, Ribeiro de Castro MC. New dressings, including tissue-engineered living skin. Clin Dermatol. 2002;20(6):715–23, 715.
83. Uccioli L, TissueTech Autograph System Italian Study Group. A clinical investigation on the characteristics and outcomes of treating chronic lower extremity wounds using the tissuetech autograft system. Int J Low Extrem Wounds. 2003;2(3):140–51.
84. Vacher D. Autologous epidermal sheets production for skin cellular therapy. Ann Pharm Fr. 2003;61(3):203–6.
85. Epicel cultured epidermal autograft instruction for use [package insert]. Cambridge, MA: Vericel Co; 2021.
86. Horch RE, Kopp J, Kneser U, Beier J, Bach AD. Tissue engineering of cultured skin substitutes. J Cell Mol Med. 2005;9(3):592–608.
87. Tego Science. Kaloderm®. Seoul: Tegoscience; 2010. [updated 2019; cited 2021 Jul 16]. http://www.tegoscience.com/eng/product/view.do?prdSeq=11.
88. Gordon AJ, Alfonso AR, Nicholson J, Chiu ES. Evidence for healing diabetic foot ulcers with biologic skin substitutes: a systematic review and meta-analysis. Ann Plast Surg. 2019;83(4S Suppl 1):S31–44, S31.
89. Samsell B, McLean J, Cazzell S, Dorsch K, Moyer PM, Moore M. Health economics for treatment of diabetic foot ulcers: a cost-effectiveness analysis of eight skin substitutes. J Wound Care. 2019;28(Sup9):S14–26.
90. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev. 2016;2(2):CD011255. https://doi.org/10.1002/14651858.CD011255.pub2. [cited 2021 Dec 21]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6464524/pdf/CD011255.pdf.
91. Álvaro-Afonso FJ, García-Álvarez Y, Lázaro-Martínez JL, Kakagia D, Papanas N. Advances in dermoepidermal skin substitutes for diabetic foot ulcers. Curr Vasc Pharmacol. 2020;18(2):182–92.
92. Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-Centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. 2015;12(6):724–32, 12.
93. Zelen CM, Serena TE, Gould L, Le L, Carter MJ, Keller J, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. 2016;13(2):272–82.
94. Kabali C, Higgins C, Guo J, Li C, Mistry J. Skin substitutes for adults with diabetic foot ulcers and venous leg ulcers: a health technology assessment, vol. 4. Ontario, CA: Ontario Health (Quality); 2021. [cited 2021 Dec 23]. 165p. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8210978/.
95. Snyder DL, Sullivan N, Schoelles KM. Skin substitutes for treating chronic wounds. Rockville, MD: Agency for Healthcare Research and Quality; 2012. [cited 2021 Nov 28]. 203p. https://www.ncbi.nlm.nih.gov/books/NBK248353/pdf/Bookshelf_NBK248353.pdf/.
96. Falabella AF, Valencia IC, Eaglstein WH, Schachner LA. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. Arch Dermatol. 2000;136(10):1225–30.
97. Aetna. Skin and soft tissue substitutes. Hartford, CT: Aetna, Inc.; 2021. [updated 2021 Dec 22; cited 2021 Dec 31]. http://www.aetna.com/cpb/medical/data/200_299/0244.html.
98. Papanas N, Eleftheriadou I, Tentolouris N, Maltezos E. Advances in the topical treatment of diabetic foot ulcers. Curr Diabetes Rev. 2012;8(3):209–18.
99. Witten CM. Promogran matrix wound dressing 510(k) summary. Rockville, MD: Department of Health and Human Services; 2002. [cited 2021 Dec 24]. 5p. https://www.accessdata.fda.gov/cdrh_docs/pdf/K014129.pdf.
100. Krause D. Kerecis 510k summary. Rockville, MD: Department of Health and Human Services; 2013. [cited 2021 Dec 30]. 6p. https://www.accessdata.fda.gov/cdrh_docs/pdf13/k132343.pdf.
101. Whitaker IS, Prowse S, Potokar TS. A critical evaluation of the use of biobrane as a biologic skin substitute: a versatile tool for the plastic and reconstructive surgeon. Ann Plast Surg. 2008;60(3):333–7.
102. Purdue GF, Hunt JL, Still JM Jr, Law EJ, Herndon DN, Goldfarb IW, et al. A multicenter clinical trial of a biosynthetic skin replacement, Dermagraft-TC, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. J Burn Care Rehabil. 1997;18(1 Pt 1):52–7, 18, 52.
103. Moustafa M, Bullock AJ, Creagh FM, et al. Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. Regen Med. 2007;2(6):887–902.