Review Article

Skin Substitutes: A Brief Review of Types and Clinical Applications

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Abstract

Replacing skin defects has witnessed several developments over the centuries. It started with the introduction of skin grafting by Reverdin in 1871. Since then, varieties of skin grafting techniques have been used successfully. Despite being clinically useful, skin grafts have many limitations including the availability of the donor site especially in circumstances of extensive skin loss, immune rejection in allogenic skin grafts, pain, scarring, slow healing and infection.[1,2] For these reasons, scientist have worked hard to find skin substitutes to replace skin defects without the need for a "natural" skin graft. These materials which are used to cover skin defects are called "Skin substitutes". This article briefly discusses the common types of skin substitutes and their clinical uses.

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Introduction

Replacing skin defects has witnessed several developments over the centuries. It started with the introduction of skin grafting by Reverdin in 1871.[1] Since then, varieties of skin grafting techniques have been used successfully.[2] Despite being clinically useful, skin grafts have many limitations including the availability of the donor site especially in circumstances of extensive skin loss, immune rejection in allogenic skin grafts, pain, scarring, slow healing and infection.[1,2] For these reasons, scientists have worked hard to find skin substitutes to replace skin defects without the need for a "natural" skin graft.

Treating wounds with "skin substitutes" dates back to 1880 when Joseph Gamgee described an absorbent dressing made of cotton wool sandwiched between layers of gauze.[3] In 1895, Mangoldt described a technique of "epithelial cell seeding" as a way of treating chronic wounds. He harvested epithelial cells by scraping off superficial epithelium from skin with a surgical blade "until fibrin exudates from the wound". He then seeded these cells onto the wounds.[1] In 1897, Lunggren recounted that fragments of skin can be kept alive when inoculated in ascitic fluid at room temperature.[4,5]

The defining moment in culturing skin was in 1975 when Rheinwald and Green successfully grew human keratinocytes on lethally irradiated murine fibroblasts.[4] In 1981, O'Conner and his group used cultured autologous epithelium to cover burn defects for the first time.[3] To construct a "living" alternative, a dermal substitute based on collagen I gel was created with mesenchymal cells such as fibroblasts. When an epidermal layer is added, this approach became known as "skin equivalent", "composite culture" or "organotypical culture."[4,5]

Commonly used skin substitutes

Tissue engineered skin refers to a material made up of cells, extracellular matrix or combination of both.[6] Skin substitutes can be classified into several types:

1. Acellular skin substitutes

1.1 Biobrane®

The use of Biobrane® skin substitute started in the late 1970s and it is now widely used as a temporary skin substitute. It consists of a nylon mesh, which acts as a "dermis" and a silicon membrane which acts as an "epidermis". Both are embedded in porcine collagen and incorporated by chemical linkage to enhance its bond to the wound base.[1,7] It is mainly used as a temporary coverage for superficial or mid-dermal partial thickness wounds, burns, donor sites and congenital diseases such as epidermolysis bullosa,[8,9] and in hydradenitis suppurativa.[10] Biobrane® virtues are its ready availability, low pain, short hospital admission time, accelerated wound healing, and buying time until skin graft material is available. However, there is a risk of infection and some studies have reported cases of toxic shock syndrome due to accumulation of exudate underneath it.[8,9]

1.2 Integra®

The Integra® skin substitute is base on work done by Yannas and Burke.[7] It is a bi-layered skin substitute made of a silicone membrane as an epidermal layer. It is impermeable to water and protects against infection. The dermal part is made of bovine collagen and shark chondroitin-6-sulphate glycosaminoglycan.[1,6,7] After coverage, the

wound becomes revascularized within 2-3 weeks.[1] At this stage, the superficial silicone layer is removed and replaced by a very thin split skin graft applied onto the neo-dermis bed. The advantages are immediate availability, allowing time for the neo-dermis formation, and good aesthetic results. However, the disadvantages are that it needs a two-step operation, being expensive, and accumulation of exudate underneath it that may lead to infection. It also needs 3-4 weeks for culture.[2,7] Integra® has been widely used in certain disaster situations such as in the management of burn victims of Pat Sin Range fire that happened on 10th February 1996 in Hong Kong.[3]

1.3 Alloderm®

The Alloderm® skin substitute is essentially formed from acellular matrix derived from a cadaveric dermis. The allodermis is processed by salt to remove the epidermis and then extracted with a solution to remove any cellular material. It is then freeze-dried to render it inert immunologically, although its basement membrane remains intact.[1,7] It has no epidermal layer. However, the acellular matrix provides a good natural medium for fibroblast and endothelial cells to regenerate from the neodermis.[6]

2. Cellular allogenic skin substitutes

2.1 Transcyte®

The Transcyte® tissue engineered skin substitute is made from a nylon mesh and a silastic semi permissible and biocompatible layer. Allogenic fibroblasts from neonatal foreskin are embedded in the mesh and allowed to grow for 3-6 weeks to produce a cellular matrix of collagen and growth factors which may enhance wound healing.[8,9] It is left in place until either spontaneous separation occurs which indicates wound bed healing or the wound is dealt with surgically.[6] It has been licensed by the FDA for use in burns.

2.2 Dermagraft®

The Dermagraft® skin substitute is similar to Transcyte® but it lacks the silicone layer and also contains viable fibroblasts. It is produced by mixing living neonatal foreskin fibroblasts with a biodegradable mesh from polyglycolic acid (Dexon or Vicryl) in a bag with circulating nutrients. The fibroblasts are cryopreserved at -80°C to maintain viability and when implanted to the wound, these start to proliferate and produce a variety of growth factors and extracellular collagen matrix components.[11] The polyglycolic acid mesh is absorbed within 3-4 weeks. It has been used effectively in vestibuloplasty after mucogingival junction and supra-periosteal dissection.[1,7]

2.3 Apligraf® (Graftskin®)

Apligraf® represents an example of a "composite skin graft", "skin equivalent' or "organo-typical skin substitute" as it has both living dermis and epidermis. The FDA approved it for clinical use in 1998 as the first true composite skin graft for the treatment of venous ulcers or neuropathic diabetic ulcers.[1,7] It is prepared by mixing living fibroblasts from neonatal foreskin with bovine collagen type I and then exposing them to heat to produce a loose matrix. Then this is left for two weeks during which time new collagen and matrix are formed giving a dense fibrous network. A suspension of living neonatal foreskin keratinocytes (from the same or different neonatal donor) is seeded on the surface of the dermal fibrous matrix and left for 4 days to proliferate and differentiate in minimally supplemented basal medium.

On the last two days, the calcium concentration is increase in the culture medium and the keratinocytes are raised to a liquid air interface to allow differentiation and stratum corneum formation for 7-10 days. At this stage, it is ready for clinical use.[2,4]

The licensed indications of Apligraf® are for the treatment of non-infected partial or full thickness venous ulcers which have not responded to conventional treatment for at least one month. It is also indicated for neuropathic diabetic ulcers that have failed to respond to conservative treatment for three weeks.[3] The clinical effect of Apligraf® may be due to both its occlusive properties and biological mediators.[12] Apligraf® has been used for treatment of venous and diabetic ulcers, and managing wounds in epidermolysis bullosa, donor sites, surgical excision of skin cancer and burns.[1,7]

3. Cellular autologous skin substitutes

Most of the previously described skin substitutes are useful in providing temporary coverage of raw skin surfaces. However, they usually need to be replaced later on by a split skin graft or re-grafting as in large wounds or by spontaneous gradual epithelialization from the wound itself in smaller wounds. In several types of wound coverage there is a need to use cultured autologous keratinocytes for permanent skin coverage. Culturing these cells is based on original techniques developed by Rheinwald and Green.[4,7]

3.1 Cultured Epidermal Autograft (CEA)

The culture of autologous keratinocytes involves taking a skin biopsy from the patient, removing the dermis and subcutaneous tissue and then mincing the epidermis with trypsin enzymes. The suspended keratinocytes are then cultured on lethally irradiated 3T3 mouse fibroblasts. The culture medium contains essential elements including epidermal growth factors.[4,7] An important point is that once cultured over a few weeks, the keratinocytes are difficult to handle and therefore they need a delivery system or a supporting dressing.[1,3] Commercially available, cultured, epidermal autografts differ in terms of their delivery or carrier systems. The

other important aspect is that keratinocytes alone may not help in full thickness wounds or burns. Therefore, blisters may develop even following small amounts of friction since the dermal epidermal junction is not completely developed. Scarring, contracture and hyperkeratosis may also develop.[7] In addition, cultured epidermal autografts are susceptible to the digestive effects of collagenase enzymes within the wound bed so the take rate is unpredictable and varies from 0-100% but is usually about 30-80%. One option to deal with this is to condition the wound bed with cadaveric allogenic skin for about four days before grafting. The allo-epidermis is then stripped away and replaced by autologous cells. Several groups have reported success using this method.[3,6]

3.2 Cultured Skin Substitutes (CSS)

From the name, cultured skin substitutes indicate grafting materials that have both epidermal and dermal components. It is an autologous graft so there is minimal risk of infection transmission. It acts as a permanent coverage. It can be handled easily and does not form blisters because the dermal-epidermal junction is well formed. However, like CEA, it takes a finite period to be prepared and it is expensive.[1,6,7] Several types were developed recently with different dermal biosynthetic scaffolds. The most commonly used type is a hyaluronic acid derived substitute.

Hyaluronic acid (Hyaluronan) is a naturally occurring polymer within the skin and it has been found to be pro angiogenic thus stimulating blood vessel growth. In contrast to collagen, hyaluronic acid is highly conserved between species. It was found first in the vitreous humor of the eye in 1934 and subsequently synthesized in vitro in 1964. It is modified by esterification to render it water-soluble.[12] Hyaluronic acid facilitates the growth and movement of fibroblasts, controls matrix hydration and osmoregulation. It is also a free radical scavenger and an inflammatory regulator.[13] Histological studies showed areas of acanthosis, continuous epidermis with interdigitation a dermoepidermal junction that resembles rete ridges.[14]

Future potential of skin substitutes

The future seems to be promising for skin substitutes. Having an artificial skin may be very helpful in many aspects. A key question, however, is how faithful is the skin substitute to the normal skin state because some studies have shown that skin equivalent keratinocytes are in an activated state?[15] This raises the theoretical possibility that such cells may have an increased risk of future malignancies or perhaps some physiological differences during wound healing or skin aging. One development for the future may be to try to recapitulate more of the properties of *in vivo* skin.

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