Skin substitutes: A review of classifications and indications for appropriate use in South Africa

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Skin substitutes have become widely accepted as a viable reconstructive option for numerous conditions, playing a substantial role in partial and full thickness skin defects ranging from acute to chronic wounds. A skin substitute has certain criteria to fulfill to be classified as such. Different classification systems have been created and adapted in this relatively new aspect of the approach to reconstruction. Some of the classifications have been aimed at making it easier for clinicians to select the best skin substitute for the type and depth of wound needed to be covered.
This article reviews some of the more readily available skin substitutes in South Africa and reviews some of the indications and makes suggestions for the appropriate use of these products. It is also aimed that this article will help improve the understanding of skin substitutes as a whole.

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Introduction

The skin is a complex, major organ fulfilling a variety of functions. It has a surface area of just under two square meters in the average adult. Each layer of the skin performs different important functions.[1] The epidermis provides a barrier against chemicals, microbes, ultraviolet radiation and prevention of water and macromolecule loss, as well as vitamin D synthesis. The dermis provides support, elasticity and compliance to the skin. The subcutaneous tissue provides shock absorption. Sensation is provided by specialist nerve endings in the skin, while temperature regulation is provided by eccrine sweat glands and blood vessels.[1,2]

It stands to reason then that a "skin substitute" (SS) needs to provide functions similar to the layer of the skin which has been destroyed or damaged. The aim of skin substitutes is to "replicate" the properties of the normal skin and offer alternatives to wound coverage in circumstances where standard therapies are not available (Figure 1). Ideally, a SS should possess the composition and function of skin or have the potential for autologous regenerative healing when applied to a wound.

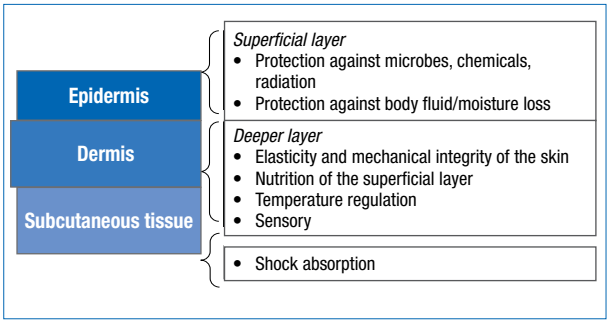

Figure 1. Diagram of the skin with the summary of properties of the two layers related to skin substitution (epidermis and dermis)

Skin substitutes can be used for coverage of a wide variety of wounds from acute wounds due to burns and trauma to chronic wounds like pressure injuries and ulcers due to venous stasis or diabetes.

The introduction of skin substitutes has:

- Improved outcomes for burn patients in terms of mortality, better functional and even cosmetic results which contribute to a better quality of life post burns.[3,4]
- Added an additional tier to the reconstructive ladder for the reconstruction of other acute and chronic wounds resulting from diverse aetiologies (Figure 2).

In recent decades the term "skin substitutes" has grown amongst the medical fraternity; however the earliest description of the use of xenograft (skin obtained from non-human origin) as a form of skin substitute was described in the 15th century BC in the Ebers Papyrus.[5] In 1503, Branca of Sicily described the first clinical use of human skin allograft (skin obtained from human origin).[6] In 1880 Joseph Gamgee described an absorbent dressing made with cotton wool sandwiched between layers of gauze that was the first tentative attempt to create a synthetic skin substitute.[6] Mangoldt, in 1895, was the first to describe the technique "epithelial cell seeding", and Lunggren, in 1897, inoculated fragments of skin in ascitic fluid.[6] In 1975, Rheinwald grew human keratinocytes on irradiated murine

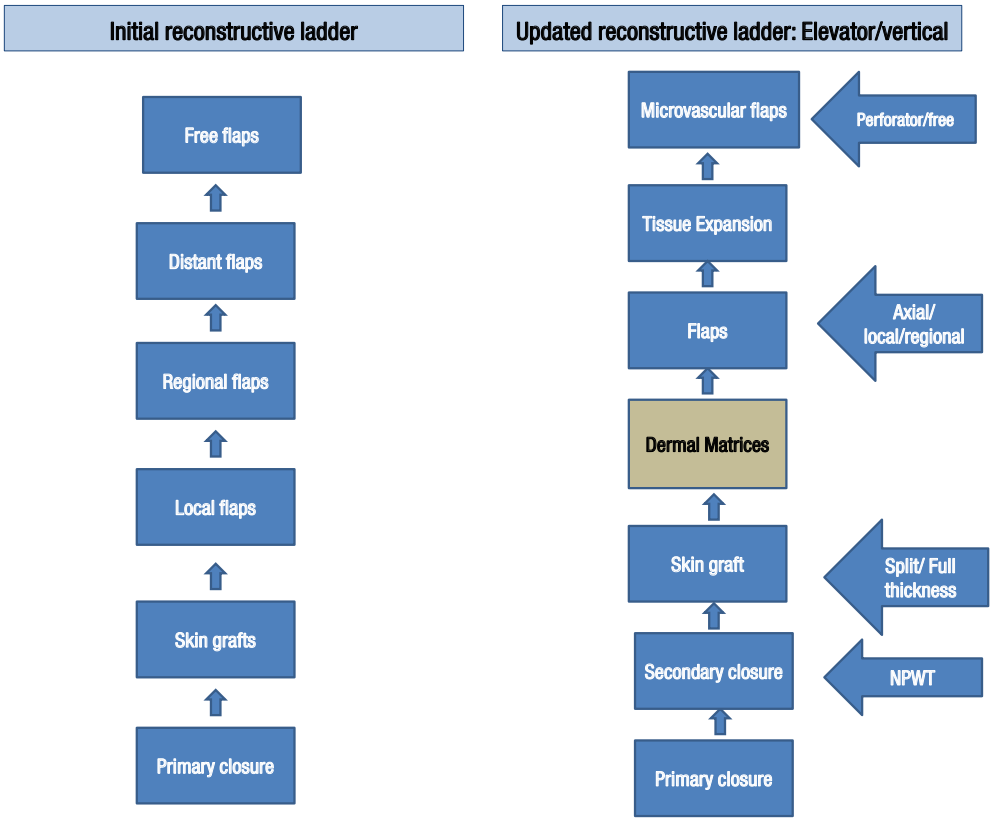

Figure 2. Diagram of the reconstructive ladder currently available for the replacement of tissue loss (adaptation from available diagrams in the literature)

fibroblasts, and in 1981 O'Conner's group used cultured autologous epithelium to cover burn defects for the first time.[6]

Various SS that were tested over time (allograft, xenograft, amniotic membrane) are still being used all over the world at burn centres. Skin allograft obtained from cadavers has proven, through the years, to be effective in preventing insensible fluid, electrolytes, and protein loss and to also act as a barrier to microbial contamination/infection. Allograft has also become indispensable in the management of patients with large total body surface area burns with inadequate donor site availability, and in countries with skin banks and availability of skin donors, the outcome of severe burns has dramatically improved. In South Africa, although a skin bank has been available in recent years, the availability of cadaver skin is restricted due to limited donation of skin from the organ donors.[7] Significant progress of biotechnology and tissue engineering has been made in the past several decades with the production and engineering of other materials for SS beyond allograft availability, and the indications for the use of allograft have currently been prioritised to the "testing" of the local wound bed for skin grafting.

A skin substitute is similar to any other medication being prescribed by a physician in that each one has its own specific characteristics and is used for different indications. An understanding of the products is therefore required for appropriate use.

This article serves to review the available definitions and classifications of skin substitutes with the aim of recommending a classification system that can be implemented to provide the necessary information about the products that are available in South Africa. This classification system must also be helpful to the members of the multidisciplinary team to promote a greater understanding of skin substitutes and ultimately ensure the correct use of each of the products.

Definitions, advantages and disadvantages of skin substitutes

Skin substitutes are a heterogeneous group of biological (derived by human or animal origin), synthetic (generated by tissue engineering), or biosynthetic (both) materials that can provide, depending on the product characteristics, temporary or permanent coverage to an area where damage to the skin has extended beyond the epidermis.[8]

Temporary skin substitutes provide protection from mechanical forces and invasion of microbes. They are a temporary measure and modulate and improve the wound bed (Table I). Permanent skin substitutes replace part of the total structure of destroyed skin components. They are incorporated into the wound bed and serve as a scaffold for the migration of cells for the formation of a new 'dermis'. They are then later covered with an autologous graft resulting in reduced scar formation and improved quality skin and less contracture.[5] Table II depicts the advantages and disadvantages of skin substitutes.

The following are general principles that a functional skin substitute should have, as outlined by Veen et al. in 2010:[9]

1. It must provide a protective barrier against pathological microorganisms and the loss of body water.
2. It must provide a biodegradable scaffold to promote the formation of new dermal tissue.

Table I. Uses for temporary skin substitutes[5]

Coverage of split thickness harvest sites
Coverage of partial thickness wounds until healing
Temporary coverage of deeper wounds to improve quality of wound bed before formal closure
Sandwich graft technique for widely meshed autologous skin grafts
Graft testing in wound readiness for grafting

3. It must allow the proliferation of cells within the scaffold that function as dermal cells instead of scar tissue; in order to achieve this, a skin substitute must promote adequate vascularisation.
4. It must be resistant against tearing forces, but still pliable enough to allow easy handling.

Besides these characteristics, an ideal SS should be able to:[5]

5. Conform to the wound surface (even or irregular).
6. Be cost effective.
7. Be widely available.
8. Have a long shelf life and be easy to store.
9. Lack antigenicity.

Table II. Advantages and disadvantages of skin substitutes

Advantages of SS
• Readily available • May be used on a poorly vascularised wound bed • Reduces or removes the inhibitory factors of wound healing • Increases the dermal component of a healed wound • Reduces the inflammatory response and subsequent scarring
Disadvantages of SS
• Higher cost (although despite high initial cost, the shortened time to wound closure can result in overall cost reduction) • Requires expertise and experience • Requires a clean wound bed (no infection or necrotic tissue)

Classification of skin substitutes

Despite many classifications being proposed for skin substitutes no single system has been universally accepted and used.

A literature review yielded several classification systems used for skin substitutes. Balasubramani et al. described three groups in 2001:[9]

Class I: Epidermal components

Class II: Dermal components

Class III: Both epidermal and dermal components

This basic classification was later replaced in 2008 by the Kumar et al. system. This system is the most commonly used skin substitute classification.[9]

Class I: Temporary and impervious dressing materials

These skin substitutes have the mechanical traits of the epidermis (prevent water loss/barrier against bacteria), even though it does not contain cellular components such as keratinocytes. It protects the wound against bacteria and prevents water loss, thereby promoting wound healing by providing a moist environment. This class is further subdivided in single- or double-layered materials. In the single-layered category, the authors included biological materials (amniotic membrane), synthetic (polymer films/foams/spray) and biosynthetic (biocellulose layers). In the bilayered category, tissue engineered materials were included.

Class II: Single layer durable skin substitutes

This class also offers two subcategories: epidermal or dermal substitutes. The epidermal substitutes in this group function as epidermis, which includes cultured epidermal cells (CEA); these tend to be associated with poor wound healing and are prone to breakdown. The dermal substitutes are similar to the dermal layer of the skin and include collagen matrix and other matrix proteins (dermal matrix) of bovine, porcine or human origin.

Class III: Composite skin substitutes

These composite SS replicate the properties of skin in its entirety by replacing the function of both the epidermis and the dermis. They are separated into human skin substitutes (allograft) and those created by tissue engineering. Many of these products have a synthetic 'epidermal' layer that is removed once cellular migration and angiogenesis occur.

This grouping as described by Kumar was later reviewed as being complicated and not to have incorporated all the products currently available on the market, or their different indications. This led to the development of a more clinically orientated classification method as proposed by Ferreira et al. in 2011.[8,9] This system uses a lettering system to describe the different products available to assist clinicians in making the best clinical decision when choosing a skin substitute (Table III).

Table III. Ferreira et al. classification of skin substitutes[8]

Layer to be replaced
Epidermal (E): the skin substitute replaces the epidermal component of the skin. Dermal (D): the skin substitute replaces the dermal component of the skin. Dermal-Epidermal/Composite (C): the skin substitute replaces both the epidermal and the dermal components of the skin
Durability or permanence
Temporary (T): a period of time is needed to improve the characteristics of the wound; the SS is replaced by an autogenous skin graft or flap. Permanent (P): restores part of the skin structure; the SS remains on the wound even after skin grafting.
Product origin
Biological (b): made from biological material; human or animal. Biosynthetic (bs): a combination of synthetic and biological components. Synthetic (s): produced in a laboratory with the aim of re-creating the skin.

More recently, Davison-Kotler et al.[9] from the Tissue Engineering and Regenerative Medicine International Society, published a new system that is inspired by factorial design. It makes provision for several features that skin substitutes possess with the intention of being helpful for clinicians as well as researchers in the biomedical field. The proposed algorithmic system does fulfill its aim of being very comprehensive and incorporates factors such as:

- Cellularity: Acellular or cellular (have added cellular components such as keratinocytes or fibroblasts).
- Layering: Single layer or bilayer.
- Replaced region: Epidermis, dermis or both.
- Materials used: Natural, synthetic or both.
- Permanence: Temporary (biodegradable) or permanent (nonbiodegradable).

According to this latest classification, an algorithm of materials allows for any possible combination of the products by combining each category cited. A product may be acellular, single layer, epidermal, natural and temporary against another one that is acellular, single layer, epidermal, synthetic (or both) and temporary or permanent. This algorithm would allow the classification of all available skin substitutes on the market.[9]

Based on the available classification systems for skin substitutes, particularly the latest one which is considered "universal", we have included in Table IV the products available in Southern Africa, as well as providing a practical approach in the application of those products as adjuncts to wound care.

Each product has its own unique characteristics and indications.

In the process of selecting a skin substitute there are many factors that need to be taken into account. We have grouped these into three different pillars for determination.[8]

1. The surgeon's experience and knowledge regarding the intended product.
2. The wound assessment:
   - Depth of defect: partial vs. full thickness
   - Aetiology of the wound
   - Desired healing outcomes: functional and aesthetic
3. Patient's factors:
   - Chronic medical conditions
   - Allergies
   - Religious considerations

The versatility of the applications for skin substitutes is well described in the literature.[6,18-20]

Reconstruction for a wide range of conditions can be achieved in acute wounds post trauma and burns; chronic wounds such as pressure injuries, venous ulcers and diabetic ulcers; for reconstruction post-contracture release after burn injuries and breast reconstruction post mastectomy and dermatological conditions such as hidradenitis suppurativa, pyoderma gangrenosum and epidermolysis bullosa.

Discussion

Due to the diverse and actively changing nature of the field of skin substitutes, there is a lack of consensus with regards to what classifies as a skin substitute and what does not. Taking into consideration the functions of the skin and definition of skin

Table IV. Classification of skin substitutes available in South Africa[7,10-17]

Product	Classification	Composition	Indication
Skin Allograft	Biological Composite (E+D) Temporary	Acellular human skin from cadaver donors, allogeneic, preserved in glycerol	Prepare for autografting in burn wounds/ trauma
Biobrane®	Biosynthetic Epidermal Temporary	Bilaminar nylon mesh filled with type I porcine collagen covered by thin lamina of silicone	Partial thickness wounds
EZDerm®	Biological Dermal Temporary	Xenograft consisting of porcine dermis collagen cross-linked with aldehyde	Partial thickness wounds
Integra®	Biosynthetic Dermal Permanent	Acellular, bilaminar bovine collagen matrix + chondroitin-6-sulphate (dermal analogous) covered by thin lamina of silicone	Partial and full thickness wounds: burns, trauma, reconstruction, exposed bone/tendons
Keragentrix™	Biosynthetic Epidermal Temporary	Acellular, bilaminar bovine type I atelocollagen peptides embedded in matrix with outer silicone film + partially embedded nylon	Partial thickness wounds Temporary cover in full thickness wounds
Matriderm®	Biological Dermal Permanent	3-Dimensional matrix of bovine collagen and elastin	Partial and full thickness wounds: burns, trauma, reconstruction, exposed bone/tendons
Nanotrix®	Synthetic Epidermal Temporary	Apo-Lactoferrin Hyaluronic Acid Polymer membrane	Superficial partial thickness wounds
NovoSorb™ BTM (Biodegradable Temporizing Matrix)	Synthetic Dermal Permanent	Biodegradable polyurethane foam (NovoSorb) bonded to non-biodegradable transparent polyurethane sealing membrane.	Deep partial/full thickness wounds, DFU, PI
Pelnac™	Biosynthetic Dermal Permanent	Acellular, single or bilaminar porcine tendon-derived atelocollagen sponge layer (covered by silicone layer if double layer) + non-adhesive silicone gauze/ TREX™ mesh (fortified/fenestrated types)	Partial and full thickness wounds: burns, trauma, reconstruction, exposed bone/tendons
Suprathel®	Synthetic Composite Temporary	Copolymer of polylactide, trimethylene carbonate and lactocapromer	Partial thickness wounds Mixed partial + full thickness

DFU: diabetic foot ulcer. PI: pressure injury

substitutes, dressings currently "classified" as skin substitutes should not be labeled as such; on the other hand, ultimately all dressings that provide support for the re-epithelialisation of the skin "could be" labeled skin substitutes.

In wounds where dermal elements are still present (partial thickness), healing occurs through re-epithelialisation (proliferation of parenchymal cells), which leads to a restoration of the original tissue. In this situation only wound coverage is needed to support this process of regeneration. Partial wounds therefore only need temporary coverage until the natural process of re-epithelialisation occurs. This can be established by temporary SS or by dressings.

In wounds where the dermis is lost (deep/full thickness), healing occurs by the proliferation of connective tissue and scar formation and contracture occurs. When dealing with this type of wound, non-secondary wound closure is needed to prevent or minimise these consequences. Materials that restore the epidermal barrier function and become incorporated into the healing wound have participation in the wound closure of deep partial and full thickness losses of the skin. Generally speaking, when a defect on the skin needs closure due to the loss of deeper layers of the skin, autologous skin grafts (autografts) and/or flaps based on the availability of donor sites should be the ideal resource for the closure of the wound. If the availability of donor sites or flaps is limited, temporary skin substitutes (Allograft, Xenograft) may be used for a period of time, or permanent skin substitutes (dermal substitutes) are an option as part of the reconstructive ladder, followed by skin grafting over the product according to its characteristics.

Through a critical review of the literature available on this matter, most of the definitions, classifications and principles of skin substitutes lead towards products that do not only support the physiological process of wound healing that occurs naturally, but *actively interact* with the wound itself. This can be established by adding cells, scaffolding or even by attracting the components that lead to the formation of new dermal elements or ensure regeneration.

SS should be distinguished from dressings through their function of actively interacting with a wound bed, promoting healing and not just supporting the process. The other difference noted is the fact that a SS, if used for the correct indication, does not need to be replaced until the desired outcome has been reached. This could be the distinguishing factor between SS and certain biological dressings.

Skin substitutes provide a new approach to managing certain challenging wounds, but they still only play a part in the greater scheme of wound management which includes specialised dressings, topical therapies, infection control, pressure care and management of co-morbidities. The understanding and application of wound care principles still remain fundamental for the closure of wounds regardless of their aetiology. Certain wounds may still have complex factors that hinder the healing process, thus skin substitutes have a place in the management of these wounds. A thoughtful assessment of the patient as a whole and the wound environment is always necessary.

Conclusion

All advances in tissue engineering of the skin have led to an improvement in the management, morbidity and mortality resulting from acute and chronic wounds, but are still not able to restore all the components and the function of skin.

Despite the rapid growth of this field, there is no ideal skin substitute available. The ideal skin substitute should be durable, autologous, vascularised and contain adnexal structures and stem cells and still needs to be developed.

The multiple classification systems available and the diverse range of products on the market have made the choice of skin substitutes complicated for clinicians not routinely using these products.

The authors hope to have provided a simplified and South Africa-specific approach to the evaluation of a wound and appropriate skin substitute selection.

Declaration of conflict of interest

The authors have no conflict of interest to declare.

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