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REVIEW ARTICLE

Severe skin issues: Skin tissue engineering only Solution

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ABSTRACT
The current trend of treatment of burn and wound injuries have shifted to a more bioengineering approach of improving the long-term function and quality of the treatment of burns and wounds. As a result of which there has been an increase in demand for various skin substitutes for the treatment of burn and wound injuries for the management of acute wound injuries as well as for the treatment post burn reconstructions. Skin substitutes could be either synthetic origin or biological origin according to the requirement of deep dermal and full thickness wounds. At present there is no ideal substitute in the market, however the current advancement in stem cell research and tissue engineering have resulted in the development of improved skin substitutes. Skin replacements offers substitution to urgent demands of sudden requirement of skin tissues. This review addresses the problems of all skin tissues and their possible solution through artificial skin engineering technique.
Keywords: *Bioengineering, Skin substitutes, Skin tissue engineering*

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INTRODUCTION

Burn and wound injuries square measure one amongst the foremost problems that the globe is addressing and also the presently on the market treatment method aren't up to the mark and square measure slow just in case of severe burn and wound injuries wherever immediate treatment is needed. As an answer to the issues of ancient treatment approach, the stress has currently shifted to a a lot of advanced and reliable bio-engineering approach.

The skin is that the largest organ within the frame. Skin is created from 3 layers, the cuticle, stratum and also the fat layer, conjointly known as the layer. The cuticle is that the outer layer of skin that keeps important fluids in and harmful bacterium out of the body [1]. The stratum is that the inner layer of skin that contains blood vessels, nerves, hair follicles, oil, and sweat glands. Severe injury to giant areas of skin exposes the human organism to dehydration and infections which will end in death. stratum may be a thicker layer of connective tissues that consists chiefly of extracellular matrix (ECM) or structural parts (such as albuminoid and elastin) that offer mechanical strength, snap and a tube bodily structure for nourishment of the skin. Cells gift inside the electronic countermeasures embrace fibroblasts, epithelial tissue cells, sleek muscle cells and mast cells. the 2 layers of cuticle and stratum square measure in constant communication with one another at numerous levels. The basement membrane (BM) may be a extremely specialized electronic countermeasures structure that physically separates the 2 layers.

The traditional ways in which of treatment of wound injuries has been to use skin grafts (autografts) from associate unknown patient or the person itself. the previous approach had several disadvantages like there is also a case once there won't be enough skin on the market and also the latter that it had a risk of rejection or infection. till the twentieth century the skin grafts were made up of the patient's own skin, however this became a tangle if the skin of the person is extensively broken as within the case of severe burns and also the patients couldn't be treated entirely with autografts.

WHAT IS ARTIFICIAL SKIN?

Artificial Skin may be a albuminoid scaffold that induces the regeneration of skin in mammals like humans. This term was initial employed in Seventies and early Eighties to explain a brand-new treatment for the case of huge burns. it absolutely was discovered that the treatment of such deep skin wounds in adult animals and humans includes the regeneration of the stratum. it's been currently commercially developed beneath the name Integra and is employed in massively burned patients for the cosmetic surgery of patients and in treatment of chronic skin wounds. [1]

Alternatively, covering is usually said skin like tissue full-grown within the laboratory, though it's still within the experimental section and is additionally said versatile semiconductor materials which will sense bit for those with prosthetic limbs (also experimental).

II.ARTIFICIAL SKIN SUBSTITUTE FOR BURN INJURY TREATMENT:

Artificial skin substitutes are divided into 2 classes: biological and artificial substitutes. The biological substitutes contain of a a lot of intact extracellular matrix like structure whereas the artificial skin substitutes square measure synthesized on demand with the assistance of tissue engineering and might be modulated advisedly in line with the necessity and performance. every category of substitutes has its own blessings and drawbacks. The biological skin substitutes square measure thought-about to be a lot of natural and appropriate one as a result of it permits glorious re-epithelialization characteristics because of presence of a basement membrane. artificial substitutes on the opposite hand show associate multiplied management over scaffold composition. the final word goal is to realize and turn out a perfect skin substitute which will exhibit a natural, effective and scar free wound healing

Definition: Skin substitutes square measure heterogeneous cluster of wound coverage materials that aid in would closure and replace the functions of the skin, either briefly or for good, reckoning on the merchandise characteristics. **[Error! Reference source not found.]**

History: The history of application of skin substitutes dates back to the primary written document on the skin graft within the fifteenth century BC as mentioned within the Papyrus of Ebers. The clinical use of human skin graft was initial delineated within the manuscript of Branca of Sicily in 1503. numerous skin substitutes that were tested over time, like human skin graft, graft and sac, square measure still getting used at numerous burn centers everywhere the globe. With the arrival and progress of biotechnology and tissue engineering, a good array of skin substitutes is currently on the market within the marketplace for the treatment of burn and wound injury.**[Error! Reference source not found.]**

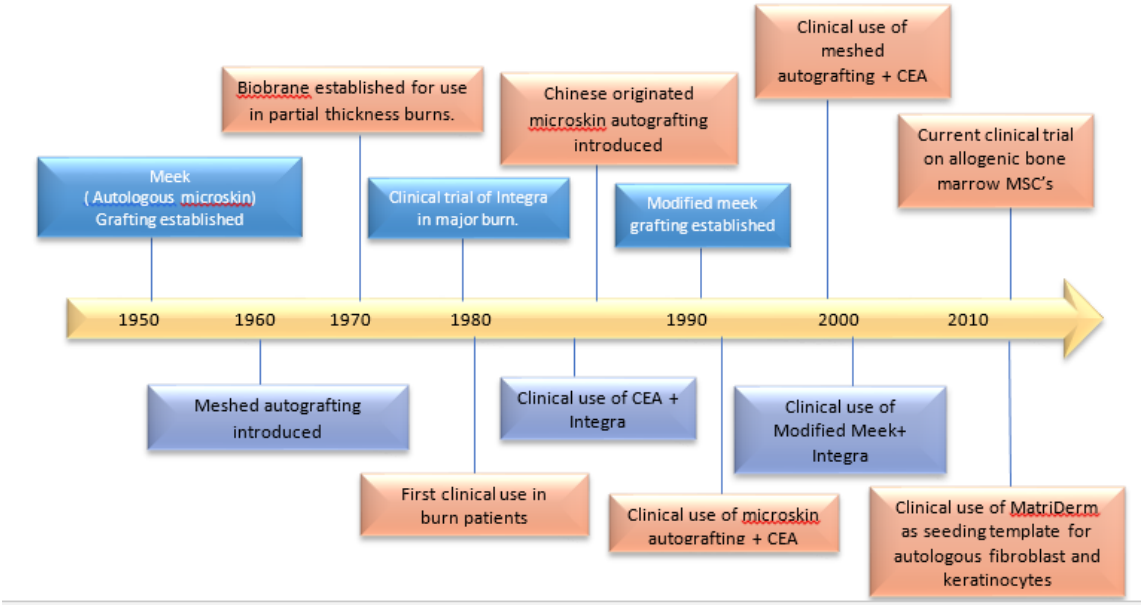


Fig. Timeline depicting the development of various skin substitutes.

ARTIFICIAL SKIN AS SKIN SUBSTITUTE FOR WOUND INJURY TREATMENT:

Wounds are basically defined as an injury to the living tissue caused by a cut, blow, or any other impact, typically the one in which the skin is cut or broken. It is of two types: one in which skin is torn, cut, or punctured (an *open* wound), or one in which blunt force trauma causes a contusion (a *closed* wound). [2]

Wound healing is a very complex and dynamic process which includes replacing devitalized and missing cellular structures and tissue layers.[2]
Cutaneous wound healing consists of three partially overlapping phases:
1. Haemostasis and Inflammation Phase
2. Proliferation Phase
3. Tissue Remodelling Phase

HEMOSTASIS AND INFLAMMATION:
Immediately following skin injury, a platelet plugs and a blood clot result in a temporary sealing of the wound, which prevents blood loss and initiates cascading molecular and cellular events leading to formation of an early, make-shift extracellular matrix that provides a scaffold for cellular attachment and subsequent proliferation. The blood clot and damaged epithelial and endothelial cells also release a variety of chemotactic factors to recruit inflammatory cells from the surrounding tissues and the circulation to the site of tissue damage. The inflammatory phase occurs shortly after injury and is characterized by the influx of inflammatory cells followed by neutrophils and then by monocyte/macrophage lineages, as well as mast cells[3].

PROLIFERATION PHASE:
As the inflammatory phase subsides, the proliferative phase of tissue repair begins by the migration and hyperproliferation of dermal and epidermal cells within the wound bed. Following the endothelial activation and degradation of endothelial basement membrane, blood-vessel sprouting occurs at the wound edge, and new vasculature develops (angiogenesis)
Formation of new blood vessels is crucial for the supply of nutrients, oxygen and metabolite exchange.In parallel to angiogenesis, fibroblasts migrate into the wound in response to platelet derived growth factor (PDGF) transforming growth factorβ1 (TGF-β1) and fibroblast growth factor (FGF), where they proliferate and produce large amounts of extracellular matrix[4].

TISSUE REMODELLING:
The tissue remodeling phase is characterized by matrix remodeling and declined cellularity. During this phase, the wound undergoes contraction, resulting in the formation of a scar with reduced tensile strength. During this phase, the initial collagen type III of the granulation tissue is gradually dominated by collagen type I, which is the main structural component of the dermis. Originally disorganized collagen fibers are rearranged, cross-linked, and aligned in parallel bundles. These processes result in the formation of a scar with reduced tensile strength and a lack of appendages[4].

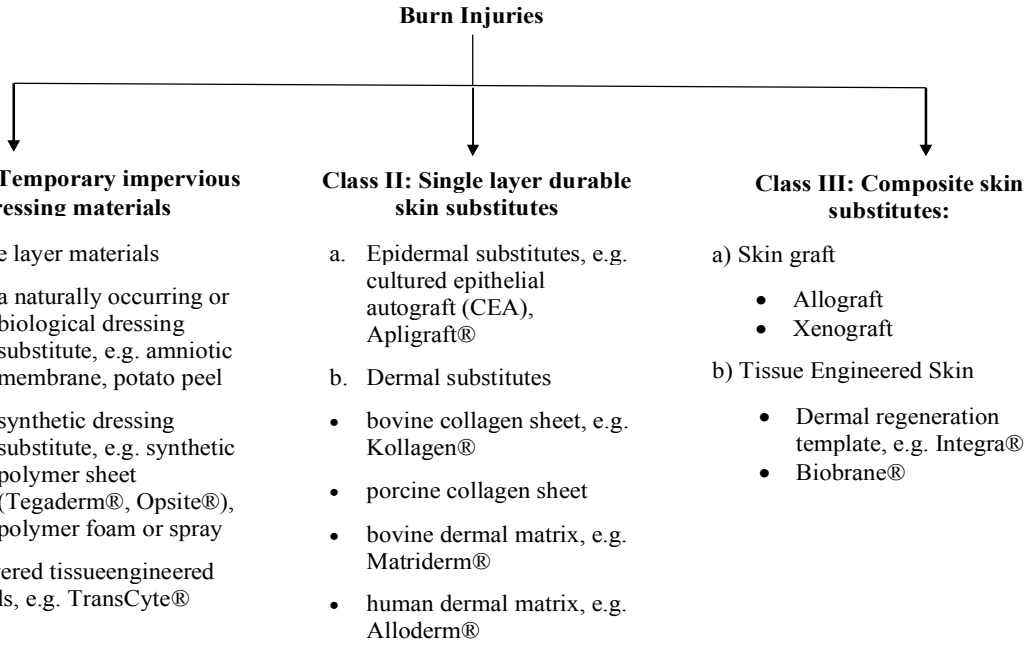
IMPORTANT FACTORS TO BE CONSIDERED FOR USE IN WOUND HEALING:
There are various important factors that are taken into consideration when the use of artificial skin substitutes for burn wound treatment comes into mind. These include the severity or depth of burn, availability of the appropriate donor, possibility of infection at the sites of skin substitution, likelihood of contracture, the relative cost incurred and the time consumption along with the experience of the skin surgeons regarding the ease and effectiveness of process. [**Error! Reference source not found.**]
The skin substitutes are capable of providing rapid wound coverage solution which require a less vascularized wound bed, increase in the quantity of dermal component in the wound, reduction or removal of inhibitory factors of wound healing, reduction in inflammatory response and subsequent causing of scars. However artificial skin substitution requires higher cost, expertise and expertise.[**Error! Reference source not found.**]

FEATURES OF IDEAL WOUND COVERAGE:
- Immediate skin repair and replacement
- Able to resist infection
- Able to prevent water loss
- Able to withstand the shear forces
- Cost effective
- Widely available
- Long shelf life and easy to store
- Lack of antigenicity
- Flexible in thickness

- Durable with long-term wound stability
- Can be conformed to irregular wound surfaces and
- Easy to be secured and applied

Classification of skin substitutes:

a) For burn injuries:



TEMPORARY SKIN SUBSTITUTES:

Temporary skin substitutes provide transient or temporary physiologic wound closure, including protection from mechanical trauma, physical barrier to foreign microorganisms and creation of a good wound environment (moist wound). [6]

The common uses of the above type of skin substitutes are:

1. for dressing on donor site for facilitation of epithelialization and pain control,
2. for purpose of dressing on clean superficial wounds until epithelialization.
3. as sandwich graft technique over the widely meshed autografts and as a "test graft" before transplantation.

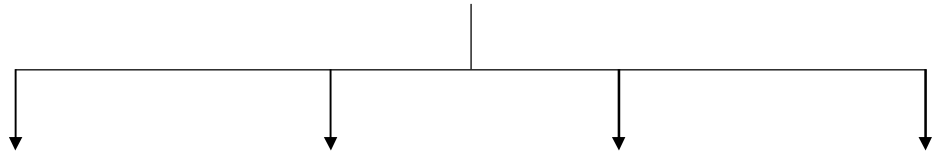
PERMANENT SKIN SUBSTITUTES:

The purpose of permanent skin substitutes is to have permanent wound closure replacing all the components of the skin and provide a higher quality of skin replacement than the normal autologous thin skin graft.

BIOLOGICAL SKIN SUBSTITUTES:

These skin substitutes which act temporarily like skin, have the advantage of being relatively abundant in supply and not expensive. While the synthetic skin substitutes can be synthesized on demand and can be modulated according tochoice, the biological skin substitutes have a more intact Extracellular Matrix (ECM) and can't be modulated so easily. They also allow excellent re-epithelialization and replacement of skin components due to presence of a basement membrane. These substitutes have a problem dealing with the slow vascularization of the skin material. The most widely used biological substitute are: cadaveric skin allograft, porcine skin xenograft and amnion.[8]

Types of Biological Skin Substitutes



i. Xenograft:

- Xenografts are skin substitutes harvested from the animals for use as temporary graft in human.
- The earliest reported xenograft application for wound coverage was at the time of 1500BC with the use of frog skin.
- The most commonly used xenograft in modern practice is porcine skin allograft.
- Xenografts are indicated for clean partial thickness

ii. Skin allograft:

- The use of skin allograft dates back to World War II.
- The cadaveric skin allograftapplication is one of the most commonly applied skin substitutes in burn wound management.
- There are two main types of cadaveric skin allografts, cryopreserved skin allograft and glycerol-preserved allograft (GPA).

iii. Amnion:

- The amnion is a thin semi-transparent tissue forming the innermost layer of the foetal membrane.
- The amnion has been used as biological dressings for burns since 1910.
- As fresh amnion carries risk contaminations and disease transmission, amnion is collected from placentae of selected and screened donors.
- It has been claimed to be one of the most effective biological skin substitutes used in burn wounds, with efficiency of maintaining low bacteria count.

iv. CEA (Cultured Epithelial Autograft)

- The culture of keratinocytes is an important advance in the burn care.
- CEA (Cultured Epithelial autografts) was first reported in the clinical use in 1981 in extensive full thickness burns.
- A large surface area of keratinocytes can be obtained from the relatively small biopsy of healthy skin from the patient.
- The autologous keratinocytes are isolated, cultured and expanded into sheets over periods of 3–5 weeks.

SYNTHETIC SKIN SUBSTITUTES:

Synthetic skin substitutes are made out of non-biological molecules and polymers that don't seem to be gift in traditional skin. These constructs ought to be stable, perishable and supply associate adequate surroundings for the regeneration of tissue. It ought to maintain its three-dimensional structure for a minimum of three weeks to permit growth of blood vessels, formative cell and coverage by animal tissue cells. Biodegradation ought to ideally turn up once this era. This method ought to occur while not large foreign body reaction as this method would increase the inflammatory response, which can be related to profound scarring. It ought to even be composed of immuno-compatible materials to avoid immunoreactive processes[8].

There are many artificial skin substitutes that ar accessible for wound coverage. However, there also are substantial range of artificial substitutes undergoing in vitro or animal testing. Amongst the artificial skin substitutes accessible within the market arBiobrane®, Dermagraft®, Integra®, Apligraft®, Matriderm®, Orcel®, Hyalomatrix® and Renoskin®.

a)**Biobrane®:**Biobrane® (Dow-Hickham, Sugarland, TX, USA) consists of associate inner layer of nylon mesh that enables fibrovascular growth associated an outer layer of silastic that is a vapour and microorganism barrier. it's been wont to provides a smart result in clean superficial burns and in donor sites. Biobrane® ought to be aloof from any full-thickness wound before skin attachment. Biobrane® is a longtime artificial dressing for burn wounds, significantly within the medicine population[9].

b)**Dermagraft®:**

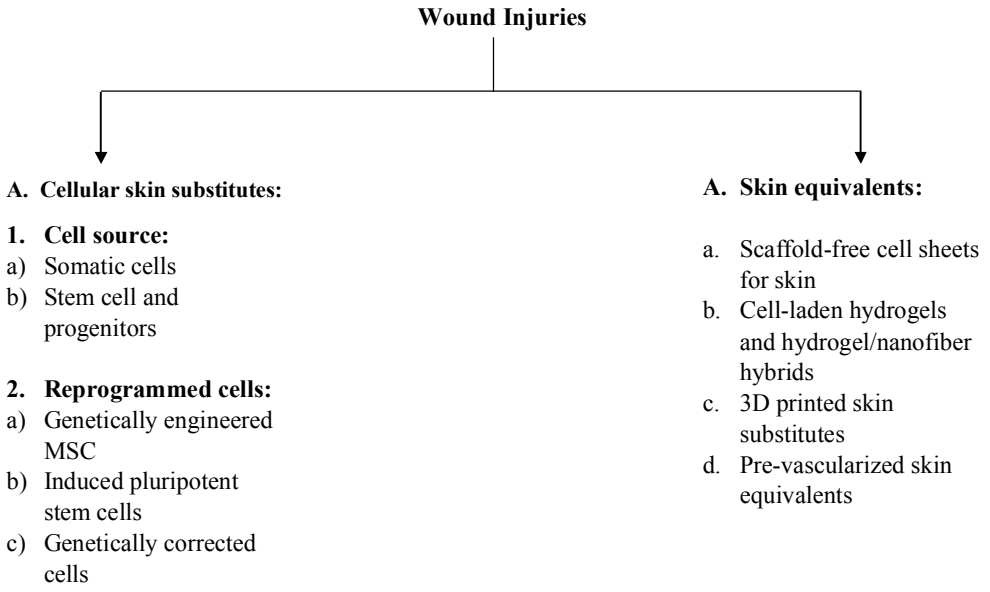
Dermagraft® (Advanced BioHealing, LaJolla, CA, USA) may be a bioabsorbable polyglactin mesh seeded with allogenic babe formative cell. Dermagraft® seems to supply results pretty much as good as transplant with relevance wound infection, wound exudate, wound healing time, wound closure and graft

take. it had been additionally reported to be removed easier than transplant, with considerably higher level of patient satisfaction. There are no adverse reactions to Dermagraft®, with no proof of rejection, early deterioration or separation from wound. There have thus far been no issues of safety concerning Dermagraft®. [9]

c)**Integra®**

Integra® (Integra Life Sciences firm., Plainsboro, NJ, USA) may be a dermal regeneration templet consisting of bovine scleroprotein, chondroitin-6-sulphate and a silastic membrane. This product has gained widespread use within the clinical treatment of deep partial-thickness wounds of chronic nature of various aetiologias. The bovine scleroprotein dermal analogue integrates with the patient's own cells and this temporary cuticular silicone polymer is in the buff away because the derma regenerates. [10]

a) For wound injuries:



A. CELLULAR SKIN SUBSTITUTES:

1.Cell supply

a) Somatic cells:

Bilayered cellular construct containing each fibroblasts and keratinocytes are developed for repair and regeneration of skin with massive wounds like burns, pressure sores, and diabetic ulcers. Fibroblasts synthesize scleroprotein and differentiation into myofibroblastic constitution to facilitate wound closure in response to paracrine signal from keratinocytes and inflammatory cells. Fibroblasts and keratinocytes communicate with one another via double paracrine signal loops, called cross speak, that ends up in the accomplishment of cells necessary for complete wound closure. once the construct applied to the wound website, the cells offer signal molecules, growth factors, and living thing matrix proteins aiding in skin tissue regeneration method.[10]

b)Stem cells and progenitors:

Most stem cells studied in wound healing ar SM, adipose-derived stem cells (ASC), epithelium primogenitor cells (EPC), and epithelial duct perivascular cells (UCPC) [M. Sasaki, R. Abe, Y. Fujita et al.]. cuticular stem cells and primogenitor cells from patient stratum also are thought of as autologous cell sources for chronic wound healing. Mesenchymal stem cells (MSC) ar a promising different for chronic wound healing as a result of which they're capable of sturdy ex-vivo enlargement whereas maintaining the flexibility to differentiate into cells of cuticular and dermal lineage. Even skin appendages like hair follicles, sweat glands, and microvessels is chop-chop regenerated within the MSC-treated wounds.[10]

2.REPROGRAMMED CELLS:

a) **Genetically designed SM:**

To amplify paracrine signal production and improve the survival of SM in an exceedingly transplantation {site|website|web website} stem cells ar genetically designed to overexpress desired therapeutic factors in wound site. The survival rate of SM genetically designed with stromal cell-derived factor-1 (SDF-MSC) in wounds was considerably high compared thereupon of traditional SM. additionally, SDF-MSC secreted

a high level of VEGF HGF and IL-6 and fashioned larger range of blood vessels in wound beds that ends up in quicker wound healing than traditional SM treatment.[11]

b) Induced pluripotent stem cells:

iPSC generates a large vary of differentiated cell sorts as well as keratinocytes and melanocytes. Keratinocyte stem cells derived from iPSC ar able to regenerate the stratum, hair follicles, associated greasy glands in an in vivo graft assay in mice. Exosomes derived from human iPSC-MSC expedited cutaneal wound healing in an exceedingly rat model through a paracrine signal, leads to accelerated re-epithelialization, reduced scar widths, and therefore the promotion of scleroprotein maturity. [12]

c) Genetically corrected cells:

Genetically corrected autologous iPSC of patients with skin diseases is used for a permanent corrective medical aid for chronic wounds ensuing from genetic predisposition. Genetic mutations is without delay repaired in iPSC victimization varied genome-editing tools, like atomic number 30 finger nucleases (ZFN), transcription activator-like effector enzyme (TALEN), or clustered, frequently interspaced, short palindromic repeats (CRISPR). [13]

CONCLUSION

Skin substitutes have important roles in the treatment of deep dermal and full thickness wounds of various aetiologias. It is evident that no single treatment can be recommended in the management and the treatment of the burn and wound injuries, but based on the recent technological advances and the various examples mentioned above the use of artificial skin as an option for treatment has seen to be emerging and being put to good use. The use of Biobrane® and CEA (Cultured Epithelial Autografts) have served as a boon to the modern society and has made treatment of burn injuries more effective and qualitatively more enhanced. Integra has emerged as another biological skin substitute that is being used for over many years now and is still proving to be useful and the ideal choice for treatment. The advance in tissue engineering and stem cell biotechnology have already led to discovery of new types of scaffolds for the production of synthetic skin substitutes which has made them more dynamic and effective and they also stand true on the tests of their performance and expected results. These advancements will surely lead to discovery of more and more skin substitutes of such kinds and would enhance the quality and the long-term function of the artificial skin graft.

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