Wound Healing and Wound Care

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1 Introduction

Understanding burn injury and its complex wound healing cascade requires recognition of the anatomy and physiology of the skin. The skin is a bilayer organ with many protective functions essential for survival.

The outer epidermal layer functions as a critical barrier composed of dead cells and keratin, which protects against bacterial and environmental toxins. The basal epidermal layer is the innermost layer of the epidermis that proliferate and divide to give rise to new cells for other epidermal layers. The undulating surface of the epidermis, called rete pegs, increases adherence of the epidermis to the dermis via the basement membrane.

The inner dermal layer has a number of essential functions, including continued restoration of the epidermis. The dermis is divided into the papillary and reticular dermis. The papillary dermis is extremely bioactive in comparison to the reticular dermis.

Superficial partial burns generally heal faster than deeper partial-thickness burns due to difference in bioactivity within the dermis; the papillary component is lost in deeper burns.

The damage or loss to the normal skin barrier functions cause the following common sequelae after burn injury:

- infection,
- loss of body heat,
- increased evaporative water loss,
- change in key interactive functions such as touch and appearance,
- excessive scarring leading to contractures.

Scars form as a result of physiologic wound healing process and may arise following any insult to the deep dermis. Genetic susceptibility, specific anatomic location, prolonged inflammation and delayed epithelialization significantly increases risk of developing excessive scarring. Hypertrophic scarring forms frequently after burn injury with incidence rates varying from 40% to 91%, depending on the depth of the wound [1, 2].

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2 Physiological Versus Pathophysiologic Wound Healing

The physiologic response to an injury to the skin in adult tissue is the formation of a scar which can be temporally grouped into three distinct overlapping phases.

- inflammation,
- proliferation,
- remodeling [3–5].

Each phase is critical to the success of wound closure. Deviations from the norm may be associated with delayed or abnormal wound healing [6].

Immediately following wounding, platelet degranulation, and activation of the complement and clotting cascades form a fibrin clot for hemostasis, which acts as a scaffold for wound repair [3].

Platelet degranulation is responsible for the release and activation of an array of potent cytokines, such as epidermal growth factor (EGF), insulin-like growth factor (IGF-I), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β), which serve as chemotactic agents for the recruitment of neutrophils, macrophages, epithelial cells, mast cells, endothelial cells, and fibroblasts [3, 7].

48–72 h after the initial event the healing process transitions into the proliferation phase which may last for up to 3–6 weeks [8]. Recruited fibroblasts synthesize a scaffold of reparative tissue, the so-called extracellular matrix (ECM). This granulation tissue is made of procollagen, elastin, proteoglycans, and hyaluronic acid and forms a structural repair framework to bridge the wound and allow vascular ingrowth [8]. Modified fibroblasts, the so-called myofibroblasts, containing actin filaments help initiating wound contraction.

Once the wound is closed, the immature scar can transition into the final maturation phase, which may last several months. The abundant ECM is then degraded and the immature type III collagen of the early wound can be modified into mature type I collagen [8] (Fig. 1).

- *The transformation of a wound clot into granulation tissue thus requires a delicate balance between ECM protein deposition and degradation, and when disrupted, abnormalities in scarring appear, resulting in excessive scar formation* [5].

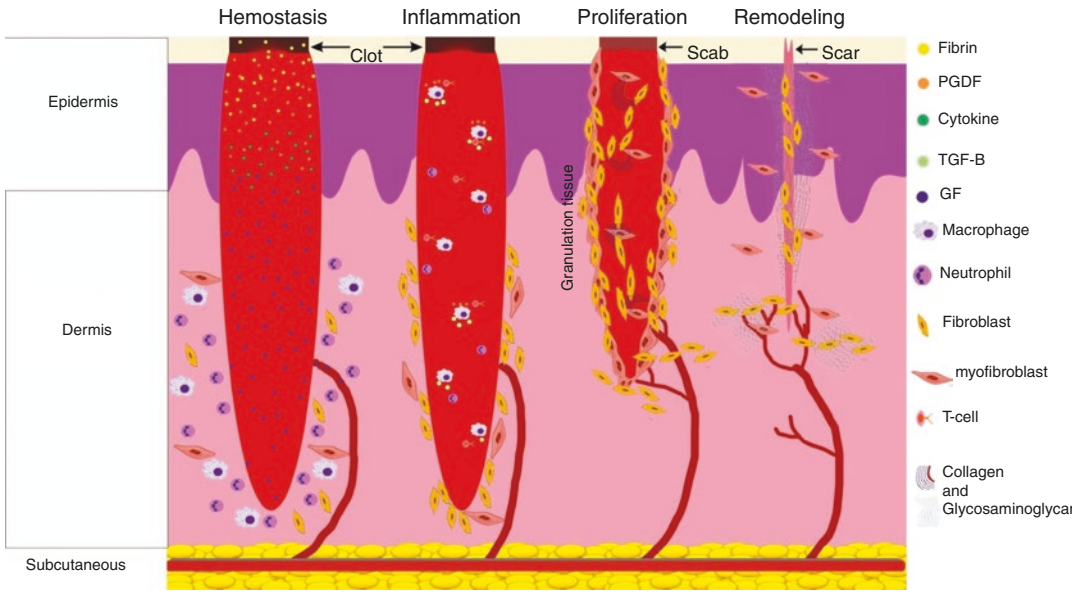

Fig. 1 Phases of wound healing

Recent evidence suggests that it is not simply the severity of inflammation that predisposes to excessive scarring but also the type of the immune response [9]. T-helper cells (CD41) cells have been implicated as major immunoregulators in wound healing.

The characteristic cytokine expression profile of the CD41 T cells represents the basis for describing either a predominantly Th1 or Th2 response to a specific or unspecific stimulus [5, 10].

While the development of a Th2 response (with production of interleukin (IL) -4, IL-5, IL-10, and IL-13) has been strongly linked to fibrogenesis, a predominance of Th1 CD41 cells has been shown to almost completely attenuate the formation of tissue fibrosis via production of interferon-gamma (IFN-γ) and IL-12 [11, 12].

2.1 Growth Factors

2.1.1 Transforming Growth Factor-Beta

Many of the biologic actions of TGF-β contribute to the normal wound healing process and have been implicated in a wide variety of fibrotic disorders [5]. Early after injury, high levels of TGF-β are being released from degranulating platelets at the site of injury, where they act as chemoattractants for lymphocytes, fibroblasts, monocytes, and neutrophils [13].

- The TGF-β family consists of at least five highly conserved polypeptides, with TGF-β1, −2, and −3 being the principal mammalian forms.
- TGF-β1 and −2 are one of the most important stimulators of collagen and proteoglycan synthesis and affects the ECM not only by stimulating collagen synthesis but also by preventing its breakdown [14, 15].
- TGF-β3, which is predominantly induced in the later stages of wound healing, has been found to reduce connective tissue deposition [16].
  - *Specifically, beyond 1 week, differential expression of TGF-β isoforms, receptors and activity modulators, rather than the mere presence or absence of TGF-β, may have a major role in the development of both, keloids and hypertrophic scarring* [17].

Interactions between keratinocytes and fibroblasts. Keratinocytes have been shown to mediate the behavior of fibroblasts during wound healing through their secretion, activation, or inhibition of growth factors such as TGF-β [9]. Particularly, release of IL-1 from keratinocytes at the wound site seems to represent the initial trigger for the inflammatory reaction and serves as an autocrine signal to fibroblasts and endothelial cells, resulting in a pleiotropic effect on them [18, 19].

2.1.2 Matrix Metalloproteinases (MMP)

The major effectors of ECM degradation and remodeling belong to a family of structurally related enzymes called MMP [5]. The MMP family consists of about 25 zinc-dependent and calcium-dependent proteinases in the mammalian system [20].

An imbalance in expression of MMPs has been implicated in a number of pathological conditions such as dermal fibrosis [21], tumor invasion and metastasis [22].

Several MMPs have been shown to mediate the breakdown of type I and III collagen, the most abundant types of collagen in the skin ECM [20]. Specifically, MMP-2 and MMP-9 activity persists after wound closure and seems to play a potent role in the remodeling process [23].

3 Wound Care Post-Burn

Treatment of burns depend on the characteristic, size, and depth of the wound. Treatments aim to expedite healing, prevent infection while minimizing patient discomfort. Burn wound therapies can be divided into three stages: assessment, management, and rehabilitation.

Management phase begins after the extent and depth of the wounds have been assessed and

wounds have been thoroughly cleaned and debrided.

Each wound should be dressed with appropriate covering that serves several purposes.

- First, it should protect the damaged epithelium, minimize bacterial and fungal colonization, and provide splinting action to maintain the desired position of function.
- Second, the dressing should be occlusive to reduce evaporative heat loss and minimize cold stress.
- Third, the dressing should provide comfort over the painful wound [24, 25].

The choice of dressing is based on the characteristics of the wound:

- First-degree wounds are minor and superficial with minimal loss of barrier function. These wounds require no dressing and are treated with topical salves to decrease pain and keep the skin moist.
- Superficial second-degree wounds will heal spontaneously, with minimal hypertrophic scarring, within 2–3 weeks if the wound remains free of infection. The capacity to heal is also dependent on the health and age of the individual. Older people and those with concomitant medical conditions are prone to delayed healing [26, 27]. These wounds need to be assessed daily and managed with dressings developed to aid in re-epithelialization, preventing wound infection, skin desiccation, and further skin damage.
- Deep second-degree and third-degree wounds will not heal and these wounds require excision and grafting.

Wound dressings can be categorized into four groups as seen in Table 1.

Table 1 Wound dressing categories

Dressing	Description	Disadvantage	Example
Conventional dressings [28, 29]	• Do not contain antibiotics or medications. • Widely used to cover clean burns to facilitate re-epithelialization	• Needs daily dressing change that can cause pain and discomfort	• Paraffin gauze • Vaseline gauze
Antiseptic and Antimicrobial dressings	• Dressings can be prepared as topical ointments or solutions • Can also be silver impregnated • Used to prevent wound infection by minimizing bacterial colonization	• Can be cytotoxic	• Sodium hypochlorite • Acetic acid • Polysporin • Povidone-iodine • Silver sulfadiazine • Aquacel AG • ACTICOAT
Biological dressings [30, 31]	• Effective in providing moisture and helps decrease bacterial load • have a more intact and native ECM structure which may allow the construction of a more natural new dermis	• Poor mechanical stability	• Amnion – Derived from human placenta
Biosynthetic dressings [32]	• Designed to use materials that simulate the function normal skin	• Expensive • Cannot be used for infected wounds • Cannot debride necrotic tissue	• Biobrane® – A temporary synthetic dressing composed of nylon mesh bonded to a silicone membrane, helps control water loss and re-epithelialization [33]. • TransCyte®

3.1 Burn Wound Excision

Methods in treating burn wounds have changed in recent decades. Most studies have shown that skin excision within 72 h after injury leads to better results such as decrease in blood loss, lower incidence of infection, shorter length of hospital stay, higher probability of graft take, and drop in mortality [34].

Early wound closure has been found to decrease severity of hypertrophic scarring, joint contractures and stiffness and promotes quicker rehabilitation [35].

In general, most areas are excised with a hand skin graft knife or powered dermatome.

In partial-thickness wounds, attempts need to be made to preserve viable dermis, whereas in full-thickness injury, all necrotic and infected tissue must be removed leaving viable wound bed of either fascia, fat, or muscle [36].

3.2 Burn Wound Coverage

Following burn wound excision, it is vital to obtain wound closure. Autografting which is the transfer of the patient's healthy skin to cover the excised burned tissue is the gold standard for burn wound coverage.

3.2.1 Skin Substitutes

With advances in burn resuscitation and critical care management, patients with large TBSA burns are surviving, leading to problems with wound coverage. This has led to the development of various biological and synthetic substrates to replace the injured skin post-burn. With the advantages of availability in large quantities, bioengineered skin substitutes, both biosynthetic and cultured autologous engineered skin, are available to provide temporary or permanent coverage [37–39].

There are different classifications of skin substitutes. The Kumar classification is the most common type. The Davison-Kotler classification is a newer type that categorizes skin substitutes based upon the following factors [39].

1. Type of biomaterials.
   (a) synthetic,
   (b) biosynthetic,
   (c) biologic,
2. Skin substitute composition regarding cellular component:
   (a) Cellular.
      - These skin substitutes consist of cells seeded within an extracellular matrix. They facilitate the release of growth factors and ECM components to enhance wound healing [40, 41].

   (b) Acellular.
      - These skin substitutes are designed to prevent fluid loss and wound bed infection. They are mainly composed of a wide range of biomaterials such as silicone, nylon mesh, acellular cadaveric dermis, and collagen [42].
3. Duration of the cover depending on its design and composition [43].
   (a) Permanent.
   (b) Semi-permanent.
   (c) Temporary.
4. Layering.
   (a) Single.
   (b) Bilayer.
5. Anatomical structure.
   (a) Epidermal.
   (b) Dermal.
   (c) Composite both epidermal and dermal components used to mimic the histological structure of normal skin [31].

Here, we will classify the skin substitutes according to anatomic structure.

3.3 Epidermal Substitutes

Act as the epidermis.

Most commonly used epidermal substitutes are cultured epithelial autografts (CEAs). These are autologous epithelial cells grown from a single full-thickness skin biopsy. These have been shown to decrease mortality in massively burned patients in a prospective, controlled trial [30]. However, widespread use of CEAs has been pri-

marily hampered by poor long-term clinical results and exorbitant costs. They have also been consistently reported to be fragile and difficult to handle even when applied on properly prepared wound beds [32, 44, 45].

There have been studies using noncultured autologous skin cell spray grafts for burns. Following application, the skin cells induce rapid epidermal regeneration achieving re-epithelialization to heal burns, donor sites, and chronic wounds. This is useful for patients having limited donor tissue availability, as well as for patients in whom the creation of donor sites may lead to significant morbidity.

Currently, commercially available autologous epidermal substitutes for clinical use include ReCell (Avita Medical Woburn, Massachusetts), Myskin (Regenerys, Cambridge, UK), (RenovaCare, Inc., NY), CellSpray (Clinical Cell Culture (C3), Perth, Australia), Epicel (Genzyme Biosurgery, Cambridge, MA, USA), EpiDex (Modex Therapeutiques, Lausanne, Switzerland), Bioseed-S (BioTissue Technologies GmbH, Freiburg, Germany), etc.

3.4 Dermal Substitutes

In contrast to cultured epidermal sheets, engineered dermal constructs can prevent wound contraction and they provide a greater mechanical stability.

To date, a wide variety of marketed dermal constructs is available. These skin substitutes can promote the healing of acute and chronic wounds by secreting extracellular matrix (ECM) proteins, a variety of growth factors and cytokines into the wound until they undergo normal apoptosis a few weeks post-implantation [46, 47].

Allografts (cadaver skin) frequently serve as skin substitute in severely burned patients. Some are chemically treated (e.g., Alloderm®), lacking the cellular elements that are responsible for the immunogenic rejection [48]. While this approach is still commonly used in burn centers throughout the world, they only provide temporary coverage. It also bears considerable risks, including antigenicity, cross-infection as well as limited availability [49].

Xenografts have been used for hundreds of years as temporary replacement for skin loss. Even though these grafts provide a biologically active dermal matrix, the immunologic disparities prevent engraftment and predetermine rejection over time [32].

Dermagraft® (Advanced Biohealing; La Jolla, CA) consists of human foreskin fibroblasts, cultured in a biodegradable polyglactin mesh [50, 51]. It stimulates ingrowth of fibrovascular tissue and epithelialization. The frozen product offers an advantage but unfortunately requires storage at −75 °C. It is thawed in sterile saline and then applied to a clean, well-debrided wound. It has a 6-month shelf life and was approved by the FDA in 2001 for full-thickness diabetic foot ulcers of more than 6 weeks' duration, extending through the dermis, but without exposed underlying structures. It has found value in healing complex surgical wounds with secondary closure.

3.5 Composite (Epidermal/Dermal) Substitutes

To date, the most advanced and sophisticated constructs that are available for clinical use. Composite skin substitutes mimic both epidermal and dermal layers of the skin. They have been shown to provide growth factors, cytokines, and ECM for host cells, thus initiating and regulating wound healing. Nevertheless, these skin substitutes are accompanied by long production time, high manufacturing cost and repeatedly fail to close the wound permanently due to tissue rejection [47].

Currently available epidermal/dermal substitutes that are in clinical use include StrataGraft (Stratatech, a Mallinckrodt Company), Epifix (MiMedx Group, Marietta, GA), MatriStem (ACell, Inc), Permaderm (Regenicis, New York, N.Y), Apligraf (Organogenesis Inc., Canton, Massachusetts, CA, USA), OrCel® (Ortec International, Inc., New York, NY, USA), PolyActive® (HC Implants BV, Leiden, The Netherlands), and TissueTech® Autograft System (Laser skin and Hyalograft 3D; Fidia Advanced Biopolymers, Abano Terme, Italy), Self-Assembled Skin Substitute (SASS) (Loex, Quebec).

These constructs are composed of autologous and allogeneic skin cells (keratinocytes and fibroblasts), which are incorporated into scaffolds.

Apligraf® was the first commercially available composite tissue analog on the market. This medical device containing living allogeneic cells was approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of venous ulcers of 1 month duration that have not responded to conventional therapy. It was approved in 2000 for neuropathic diabetic ulcers of more than 3-week duration [52]. The epidermal component of this bilayer skin construct consists of neonatal foreskin keratinocytes seeded on a dermal component comprised of neonatal foreskin fibroblasts within a matrix of bovine type I collagen.

Orocel®, the first biologic cellular matrix, was initially developed in 1971 as a treatment for dystrophic epidermolysis bullosa [53].

Self-Assembled Skin Substitute (SASS) is a reconstruction of a fully autologous bilayered skin substitute without using any exogenous scaffold or biomaterial. SASS requires a 31-day production period [54, 55].

Integra® was developed in 1981 and approved by the FDA in 2002. It is a bilaminar skin equivalent composed of porous matrix of cross-linked bovine collagen and shark-derived glycosaminoglycan, attached to a semipermeable silicone layer that serves as an epidermis. The membrane helps prevent water loss and provides a flexible wound covering, while the scaffolding promotes neovascularization and new dermal growth. Cells migrate into the matrix while the bovine collagen is absorbed and replaced by the patient's dermal elements. Rebuilding of the scaffolding occurs within 2–3 weeks, at which time the silicone layer is removed, allowing re-epithelialization from the wound edge. Complete wound closure takes approximately 30 days. Indications for Integra include pressure, diabetic, chronic vascular and venous ulcers, as well as surgical wounds and has been successfully utilized in immediate and delayed closure of full-thickness burns, leading to reduction in length of hospital stay, favorable cosmetics, and improved functional outcome in a prospective and controlled clinical study [56–60]. Our group previously conducted a randomized clinical trial utilizing Integra® in the management of severe full-thickness burns of ≥50% TBSA in a pediatric patient population comparing it to standard autograft-allograft technique, and found Integra to be associated with improved resting energy expenditure and improved aesthetic outcome post-burn [61]. It has also been found to inhibit scar formation and wound contraction [62].

There are also newer skin substitutes available in the market (Table 2)

Table 2 New skin substitutes

Skin substitutes				
Type	Subtype	Name	Composition	Reference
Epidermal	Cultured epithelial autograft (CEA)	Epicel (Genzyme tissue repair Corp, Cambridge, Massachusetts)	CEA from human keratinocytes embedded in fibrin mesh. Disadvantage is the high cost, limited reliability, fragility, susceptibility to infections, complex post op care	[30, 32, 44, 45]
	Autologous skin suspension ASCS or cell spray	Recell (Avita medical Woburn, Massachusetts)	Autologous skin suspension that is produced using minimal donor skin and applied as a cell spray. Induces rapid re-epithelialization and wound healing	[83, 84]
		MySkin (Regenerys, Cambridge, UK)	Suspended CEA delivered as spray to promote re-epithelialization	[85, 86]
		Skin gun (RenovaCare, Inc., NY)	Expansion ratio of skin donor site to treatment surface area of about 1:20	[87]
		Keraheal (Seoul, Korea, MCTT)	Suspension form of cultured epithelial cells plus fibrin glue to facilitate epithelial cell attachment	[88]

(continued)

Table 2 (continued)

Skin substitutes				
Type	Subtype	Name	Composition	Reference
Dermal		Abwat (advanced wound bioengineered alternative tissue—Superficial, Aubrey Inc. Carlsbad, California)	Made of porcine collagen type I embedded in a nylon mesh and a porous silicone membrane	[89]
		OASIS wound matrix (Healthpoint ltd., Ft worth, Tex)	Derived from the submucosal layers of the porcine intestine. Contains glycosaminoglycans and growth factors	[90, 91]
		Matriderm (skin and health care AG, Billerbeck, Germany)	Made of type I collagen fiber coated with 3% a-elastin hydrosylate matrix. Can be used as one-stage procedure with STSG.	[92]
		Biodegradable temporizing matrix, BTM (PolyNovo, Melbourne, Australia)	Composed of biodegradable polyurethrane foam plus a temporary nonbiodegradable polyurethrane seal. Fully synthetic, making it cheaper to produce	[93]
		Matristem (Acell, Inc., Columbia, MD, USA)	Composed of extracellular matrix derived from porcine urothelium. Provides barrier protection	[94]
		Integra (LifeSciences, Plainsboro, NJ, United States)	Bovine collagen matrix with a silicone layer. Most studied dermal replacement matrix	[10, 14]
		Alloderm (LifeCell, Branchburg, N.J.)	Human cadaveric acellular matrix	[48, 49]
		Suprathel (Polymedics, Atlanta GA)	Synthetic copolymer >70% DL-lactide polymerized with ε-caprolactone and methylenecarbonate	[93]
Composite		Permaderm (Regenicis, New York, N.Y)	Autologous fibroblasts and keratinocytes embedded with collagen and glycosaminoglycan substrates	[95]
		Self-assembled skin substitute (SASS) (Loex, Quebec)	Reconstruction of a fully autologous bilayered skin substitute without using any exogenous scaffold or biomaterial. Requires a 31-day production period [28, 29].	[54, 55]
		Epifix (MiMedx group, Marietta, GA)	Composed of dehydrated amniotic and chorionic membrane containing collagen, connective tissue, cytokines, and growth factors	[96]
		SkinTE (PolarityTE, Salt Lake City, UT)	An autologous homologous skin construct derived from full-thickness skin	[97]
		Cultured skin substitute (Cincinnati, USA)	Autologous keratinocytes and fibroblasts from patient biopsy, combined into a bilayer with bovine collagen matrix	[98]

4 Adjuncts

To further stimulate healing, several adjuvant treatment methods have been developed.

4.1 Negative Pressure Wound Therapy (NPWT)

NPWT is a wound dressing system than continuously or intermittently applies subatmospheric pressure to the surface of the wound. NPWT has been commonly used in various acute and chronic wounds [63, 64]. Majority of published literature on the use of NPWT for burns is on the use of NPWT used in skin grafting to bolster the grafts which helps promote the growth of granulation tissue → increasing the success rate of graft take. There are a few studies *on the use of NPWT on acute burn and* there is promising evidence to suggest NPWT may reduce edema and wound progression [65–67].

NPWT promotes healing through exudate removal, increase in tissue perfusion, and by exerting tensile forces on the local tissue environment; they create cellular deformation that results in mitotic activity and cell proliferation [68, 69]. NPWT is contraindicated on wounds with exposed vessels, malignancy, necrotic tissue, and untreated osteomyelitis [70, 71].

4.2 Hyperbaric Oxygen (HBOT)

HBOT is a treatment modality that has been used as an adjunct in wound healing for over 40 years. The patient undergoes multiple treatments lasting for 60–120 min inside a sealed chamber with 100% pressurized oxygen at 1.5–3 atmospheres absolute (ATA) [72].

Recent studies have shown that HBOT is safe and effective for improving burn wound healing by improving tissue oxygen and phagocytosis, preventing dermal ischemia, reducing edema, modulating the zone of stasis, preventing partial- to full-thickness conversion, and preserving cellular metabolism [73–75]. HBOT has been demonstrated to be safe and effective. However, more data are needed before broad conclusions can be made about the overall utility of hyperbaric oxygen for treating burns [76, 77].

5 What's Next?

There are multiple ongoing clinical trials on the use of new skin substitutes in the treatment of burn injuries. One of the interesting focus of bioengineering and regenerative science is on the use of stem cells and the development of the 3D skin printer.

5.1 Stem Cells

The influence of stem cells on wound healing is very promising. Mesenchymal stem cells (MSCs) enhance wound healing through differentiation and angiogenesis. They also regulate the immune response and inflammation [78]. Preclinical and clinical trials show that MSC therapy accelerates wound closure [79].

5.2 3D Skin Printing

A solid 3D structure is made through a 3D printer by sequentially delivering thin layers of materials and bonding them together [80]. For 3D skin printing, this involves delivery of cells layer by layer, along with scaffolding materials using a microfluidic cartridge over the burned area. The use of 3D bioprinting is quite promising. However, there are still a lot of technological and regulatory challenges that need to be overcome [81, 82].

6 Summary

Loss of the normal skin barrier function causes the common complications of burn injury. These include infection, loss of body heat, increased evaporative water loss, and change in key interactive functions such as touch and appearance. Excessive scar formation in the areas of a deep dermal burn represents an additional well-known side effect that significantly affect the patient's quality of life, both physically and psychologically.

Early excision and early closure of the burn wound has been probably the single greatest advancement in the treating patients with severe thermal injuries during the last 20 years. Despite all efforts, an off-the-shelf, full-thickness skin replacement is not yet available. A future prospective is to incorporate cellular growth-enhancing substances or additional cell types, besides keratinocytes and fibroblasts, in the bioengineered skin substitutes to obtain constructs with improved function and higher resemblance to native skin. The development of gene transfer technology and the use of stem cells appear to be a promising means in this context.

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