WOUND HEALING CONCEPTS: CONTEMPORARY PRACTICES AND FUTURE PERSPECTIVES

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ABSTRACT
The advancements in the development of wound dressings have seen tremendous growth in the past few decades. Wound healing approach has majorly shifted from dry healing to moist healing. There has been a significant advancement in our understanding of the underlying physiology involved in wound healing and the associated systemic factors having a direct or indirect influence on the healing. This has resulted in the development of wound dressings designed to treat specific types of wounds. The present review discusses the physiology of wound healing, followed by different factors that contribute to healing. The advancements in wound dressings with their merits and limitations, newer approaches in wound care i.e., hyperbaric oxygen, negative pressure therapy, skin substitutes and role of growth factors in wound healing, have been highlighted. In addition, more recent approaches for effective wound care like smart devices with sensing, reporting and responding functions are discussed.

Keywords: Wound healing, Moist healing, Skin substitute, Negative pressure therapy

INTRODUCTION
The skin is an intricate structure composed of the epidermis and dermis, including the subcutaneous fat or dermal adipocyte layer. The skin also protects the underlying organs, a function necessary for the survival of the organism [1]. The epidermis consists of keratinocytes and it protects the body from the outside environment. The dermis consists of collagen fiber, blood vessels, sweat glands, and hair. Subcutaneous fat stores nutrients and prevents heat from escaping the body [2] (Fig. 1).

Skin wounds
Skin wounds are the result of the disruption of the normal anatomic structure of skin hence affecting their function [3]. A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or because of the presence of an underlying medical or physiological condition [4]. Wounds can be classified on the basis of nature of healing process, the number of skin layers and area of skin involved.

Based on the nature of healing process, wounds are classified as acute and chronic. Acute wounds are mainly caused due to superficial mechanical injuries like friction and abrasion. Clean penetrating wounds caused by knives or surgical incisions and superficial burn wounds can also be classed as acute. These tissue injuries heal completely, with minimal scarring within the expected time frame, usually 8–12 w without complications. Chronic wounds are a result of tissue injuries that heal slowly, generally healing period prolonged beyond 12 w. These wounds if not healed completely also have issues of recurrence. The non-healing nature of such wounds is usually due to underlying physiological conditions like diabetes, deficiencies, malignancies, persistent infections and other patient-related factors [2, 4].

Wounds are also classified based on the number of skin layers and the area of skin affected. Superficial wounds are injuries affecting only the epidermal layer. Injuries affecting deeper dermal layers, including blood vessels, sweat glands and hair follicles are referred to as partial-thickness wounds. Full-thickness wounds are those affecting underlying subcutaneous fat or deeper tissues in addition to the epidermis and dermal layers [4].

Wound healing
Wound healing is a highly complex physiological process involving the involvement of various cells and biochemical components. The
The entire healing process is accompanied by activation of several enzymatic pathways which ultimately help the tissue to heal [5]. The process involves regeneration and replacement of damaged tissues. The healing progresses through a series of interdependent and overlapping phases that help in replacement of lost tissue and re-establishment of tissue integrity. The different stages involved in wound healing are hemostasis, inflammation, migration, proliferation and maturation phase [3, 5, 7]. The events occurring during these phases are depicted in fig. 2.

Factors affecting wound healing

Factors affecting wound healing can be categorized as local and systemic. Factors that have a direct influence on the healing of the wound are classified as local factors. Other factors that are not directly located at the wound site but have an influence on the healing are classified under systemic factors [6, 8, 9]. The local and systemic factors affecting wound healing are summarized in table 1.

### Table 1: Local and systemic factors affecting wound healing

| Factors affecting wound healing | References |
|---------------------------------|------------|
| **Local**                       |            |
| Oxygenation                     | [10-13]    |
| Infection                       | [14-16]    |
| Maceration                      | [18-19]    |
| Necrosis                        | [20]       |
| Trauma                          | [21]       |
| Oedema                          | [21]       |
| Desiccation                     | [22, 23]   |
| **Systemic**                    |            |
| Age                             | [24-26]    |
| Stress                          | [27, 28-31]|
| Ischemia                        | [32]       |
| Diseases                        | [33]       |
| Obesity                         | [35]       |
| Medications: glucocorticoid steroids, NSAID’s | [36] |
| Alcoholism and smoking          | [37, 38]   |
| Immuno-compromised conditions: Cancer, radiation therapy, AIDS Nutrition | [9, 50] |

**Local factors**

**Oxygenation**

Oxygen is critical for all stages of wound healing. Healing tissue also has an increased energy demand. The mitochondrial enzyme cytochrome oxidase requires oxygen for energy metabolism i.e., production of high-energy phosphates for various cellular functions. The process of collagen synthesis involves the production of procollagen, followed by collagen maturation. Oxygen is involved in the hydroxylation of proline and lysine into procollagen. The phase of angiogenesis is initiated by hypoxia. But reports suggest that the administration of oxygen can accelerate and sustain the growth of blood vessels. Oxygen also exhibits antimicrobial activity. Leukocytic NADPH oxidase converts oxygen to a superoxide ion which kills bacteria [10-13]. Overall, the effects of oxygenation on tissue healing are summarized in fig. 3.

**Infection**

Based on the state of replication of microorganisms, wound infections can be classified as:

- Contaminated—presence of non-replicating organisms on a wound
- Colonization—the presence of replicating microorganisms on the wound without tissue damage
- Local infection/critical colonization—microorganism replication and the beginning of local tissue responses
- Spreading invasive infection—the presence of replicating organisms within a wound with subsequent host injury [1-4, 16].

Inadequate control measures to manage infected wounds can lead to cellulitis (cell inflammation) and, ultimately, bacteremia and
Wound healing is generally delayed in the elderly due to various factors. Age, systemic factors, and trauma can all play a role in delayed healing. In the presence of scab tissue that forces epithelial cells to burrow, epithelialization is drastically slowed. Desiccation and maceration can also hinder the healing process. Necrosis, a non-viable, devitalized tissue, can impede the healing process. Trauma and blood supply can further delay healing. Desiccation can occur when wounds are exposed to excessive amounts of liquid, leading to the elevation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF-α, which can further delay healing. In addition, psychosocial factors, such as stress, can significantly impact wound healing. Psychological stress can lead to clinically relevant delays in wound healing, as stress increases levels of glucocorticoids leading to suppression of inflammatory and immune responses. Ischemia, which can be caused by a variety of conditions, can also delay healing. Obesity, diabetes, and sepsis, among other conditions, can lead to impaired wound healing. Medications, such as corticosteroids, NSAIDs, and antihistamines, can also affect wound healing. The overall immunity is declined making the wounds more vulnerable to microbial contamination. The factors that complicate the healing process in older patients include nutritional deficiencies, altered hormonal responses, poor hydration, and conditions like diabetes mellitus, heart disease, and peripheral ischemia. All phases of wound healing are compromised, including decreased inflammatory and proliferative responses, delayed angiogenesis, delayed remodeling, and slower re-epithelialization.
Moist wound dressing can fall under one of the following three categories:

- **Dry dressing**
  - Cotton wool
  - Lint
  - Gauze

- **Moist dressing**
  - Polyurethane films and foams
  - Alginate
  - Hydrocolloid

- **Advances**
  - Growth factors
  - Skin substitutes
  - Hyperbaric oxygen
  - Negative pressure wound therapy

### Table: Examples of drug classes that delay different phases of wound healing

| Class of drugs   | Effect on wound healing                                                                 | References |
|------------------|----------------------------------------------------------------------------------------|------------|
| Chemotherapeutic drugs | Detrimental effect on the rapidly divided tissues of healing wounds reduced angiogenesis | [37-40]    |
| Antihistamines   | reduced tensile strength of wounds negative impact on fibroblast function              | [41]       |
| Anticoagulants   | Decreased tensile strength of wounds reduced collagen synthesis                        | [42]       |
| NSAID’s          | Reduced inflammatory response, excessive wound scarring, antiproliferative effect on blood vessels | [43]       |
| Immunosuppressant | Decreased tensile strength in wounds, reduce WBC counts, reducing inflammatory activities and increasing the risk of wound infection | [44, 45]  |

### Alcoholism and Smoking

Alcohol has been reported to affect all the phases of wound healing with compounded wound healing problems. There is a reduction in pro-inflammatory cytokines and neutrophil function. Alcoholism is associated with a decrease in the rate of wound closure and suppressed angiogenesis, decreased collagen synthesis, and an overall reduction in the tensile strength of the wounds [46]. Smoking causes an overall reduction of tissue oxygenation, reduced collagen synthesis and epithelialization, reduction in lymphocyte and neutrophil functions, and suppressed proliferation of WBCs. These effects result in poor wound healing and an increased risk of opportunistic wound infection [47]. Vitamin C acts as a co-factor for the proline and lysine hydroxylases that stabilize the collagen molecule. According to reports, Smokers have depleted vitamin C levels compared with non-smokers. Smoking cessation can improve the levels of serum collagen with an associated improvement in wound healing and collagen formation [48, 49].

### Nutrition

Healing of wounds requires an adequate supply of nutrients. All cellular activities require energy for which diet is the major source. Carbohydrates are the principal source of energy for the body and help sustain the high metabolic activity required for regeneration. Adequate levels of protein are necessary for repair and replacement of tissue. Increased protein intake is particularly important for wounds where there is significant tissue loss requiring the production of large amounts of connective tissue. Protein deficiencies have been associated with poor revascularization, decreased fibroblast proliferation, reduced collagen formation, and immune system deficiencies. Fats provide energy for proliferation. They are the building blocks for the regeneration of epidermal and dermal tissues. Lipids are important for cell membrane synthesis, epithelial phospholipids, inflammatory reactions, and intracellular matrix synthesis. In addition to protein, carbohydrates and lipids, wound healing also requires the presence of micronutrients like Vitamins (A, B complex, C, E, and K) and Minerals (copper, iron, zinc) [9, 50].

### Wound dressings

Wound healing is a complex physiological process and requires a suitable environment that promotes healing. Over the years, several wound healing products have been developed that facilitate one or more phases involved in wound healing. Wound dressing is a material designed to be in contact with the wound and hence differentiated from a bandage that merely holds the dressing in place [51]. An ideal wound dressing would be one which is capable of maintaining the optimum moisture at the wound surface while at the same time being capable of absorbing excess exudates from the wound and hence preventing maceration. The dressing should maintain a sufficient exchange of gases and should be impermeable to bacteria. The other characteristics that are desired would be non-toxic, non-allergic, free from contaminants, not necessitating frequent dressing changes, cost-effective, and comfortable [52].

Technological advancements in wound dressings have seen changes from crude applications of plant herbs, animal fat, and honey to tissue-engineered scaffolds. Some of the reported plant extracts for wound care include Guiera senegalensis, Commmelia diffusa, Spathodea campanulata, Trichophyton species etc. [53]. Honey has been used for thousands of years and is still part of many advanced wound dressings [54]. For several years, traditional wound care products focus on drying the wound site by using absorptive gauzes. Drying resulted in the formation of a crust or scab that usually would fall off as the wound healed. This led to scarring and susceptibility to secondary infection and skin damage in the process of the crust coming off. However, it has now been shown that having a warm moist wound environment achieves more rapid and successful wound healing. It was revealed that the wound is healed twice as fast with an appropriate amount of moisture compared to when dry. Also, the exudate contains much of the growth factors which are necessary for skin regeneration [2, 51, 55].

### Dry dressings

Traditional wound dressings are regarded as passive devices that intend to protect the wound from further injury. Dressings under this category include natural or synthetic materials like cotton wool, lint, gauze, knitted viscose, and tulle dressings. These dressings absorb the exudate at the wound site and keep it dry. They also prevent the entry of harmful bacteria. Moreover, these materials adhere to the desiccated wound surface inducing trauma on removal [2, 4, 51].

### Moist wound therapy

The greatest advantage of these dressings is the maintenance of a moist environment at the wound surface. These modern dressings come with other advantages like decreased pain, requiring fewer dressing changes, and reduction in scarring [2, 56]. Advancements in wound dressings over the years have been outlined in fig. 4.

**Fig. 4: Advancements in wounds dressings**

- Dressings that maintain existing levels of tissue moisture—Example: Polyurethane films and hydrocolloids
b. Dressings that absorb excessive wound exudate—Example: Foam dressings and alginate-based dressings

c. Dressings that add moisture to the tissues—Hydrogel dressing [22]

Moisture maintaining dressings

Polyurethane film dressings

These consist of a thin, semipermeable polyurethane film (fig. 5) coated with an adhesive layer enabling the dressing to adhere to intact skin and can stay in place for up to 7 d. The semipermeable nature allows water vapor transmission, which can vary from 300 g/m²/24 h to 800 g/m²/24 h. They protect against bacteria and help in retaining moisture at the wound surface. They do not absorb exudates. Film dressings provide a protective environment, which is impermeable to bacteria and liquids and can stay in place for up to 7 d. They have limited application as a primary dressing wherein they are indicated only for dry and superficial wounds. For heavily exuding wounds, they can be used as a secondary dressing on top of dressing pads or foam dressing [6, 57].

Fig. 5: Polyurethane film dressing [58]

Hydrocolloid dressings

These are occlusive dressings that are capable of maintaining the natural moisture levels of the regenerated tissues. Similar to film dressings (fig. 6) discussed in the previous section, these also do not have the property of active moisture absorption. The dressing is permeable to air and water vapor but impermeable to fluids and microorganisms [22, 59].

Fig. 6: Hydrocolloid dressing [60]

Moisture absorbing dressings

In cases where wounds generate moderate to high levels of exudate, an absorbent dressing is needed. Absorbent dressings are those types that have a high capacity for capturing and holding fluid. Included under this category are hydrophilic foams and alginites that are capable of absorbing fluid almost 20 times their weight [59]. Compared to non-absorbent dressings, they require fewer dressing changes and hence enable undisturbed wound healing [22].

Foam dressings

Foam dressings are generally made from semipermeable polyurethane (fig. 7). They create a moist environment, conducive to wound healing. They are also non-adherent, impermeable to bacteria and other contaminants but permeable to water vapor. They are available as pads, sheets, and cavity dressings [55, 59].

Calcium alginate dressings

Alginate dressings are commercially available as pads (fig. 8) ropes or ribbons. These are highly absorbent and get converted to a gel by absorbing the wound exudates. The dressings can be occlusive to semi-occlusive and suitable for wounds that produce moderate to large amounts of exudates. Using them on wounds with minimum exudates has a chance of drying out the wound bed. Alginites also have haemostatic properties. They have also been suggested to promote healing via a direct modulatory effect on wound macrophages [62-65].

Fig. 7: Polyurethane foam dressing [61]

Fig. 8: Calcium alginate dressing [66]

| Table 4: Marketed wound dressings |
|-----------------------------------|
| Type of wound dressing            | Examples of commercially available dressings                          | References |
| Dressings that maintain existing  | Polyurethane films                                                    | [4, 57]    |
| levels of tissue moisture          | Hydrocolloids                                                          |
| Dressings that absorb excessive    | Alginites                                                              |
| wound exudate                      | Hydrogels                                                              |
| Dressings that add moisture to     | • Alginate Based                                                       |
| the tissues                        | • Collagen-based hydrogel                                              |
|                                    | Opsite®, Tegaderm®, Bioclusive®                                       |
|                                    | Granuflex®, Confeel®, Tegasorb®                                       |
|                                    | Lyofoam®, Allevyn® and Tiele®                                         |
|                                    | Sorbsan®, Kaltostat®, Algisite®                                       |
|                                    | Nu-Gel®, Tegagel®, Algosterr®, KytoCel®, Chitoderm®, Chitermin® plus  |
|                                    | GellerateRX®, Regeneracare® Wound Gel                                  |
|                                    | Bioengine®Collate®                                                    |
Dressings that add moisture to the wound bed

Hydrogels

Hydrogels are vasty hydrophilic macromolecular networks, which are produced by chemical or physical crosslinking of soluble polymers [67]. They contain 90% water and 10% natural or synthetic polymers. Hydrogel-based wound dressings (fig. 9) are one of the most promising materials in wound care, fulfilling important dressing requirements, including (a) keeping the wound moist whilst absorbing extensive exudate, (b) adhesion-free coverage of sensitive underlying tissue, (c) pain reduction through cooling, (d) permeable nature allowing an exchange of gases and water vapor and (e) they possess tissue-like structure and compatibility [68]. Their main disadvantage is their poor mechanical stability at swollen state, which can be addressed by using composite hydrogel membranes [67].

![Fig. 9: Hydrogel dressing](image)

Advances in wound dressings

Growth factors

Growth factors are endogenous signaling molecules that regulate cellular responses for the wound healing processes of migration, proliferation, and differentiation. Some of the important growth factors involved in wound healing are PDGF, EGF, VEGF, EGF, TGF-α, IGF, bFGF, KGF, and TGF-β1-3 [70]. Growth factors can be delivered by incorporating them into hydrogels (cellulose, chitosan, or synthetic polymer-based), scaffolds (collagen, chitosan, and hyaluronic acid-based), particulate systems (microparticles, nanoparticles, and liposomes) and miscellaneous systems (integration with charged molecules) [71, 72].

![Fig. 10: Negative pressure wound therapy](image)

Skin substitutes

Skin substitutes provide a replacement for the extracellular matrix and accelerate the healing of both acute and chronic wounds. Artificial skin substitutes are often compared with split-thickness skin autografts, which are considered as the ‘gold standard’ for skin substitutes. Skin substitutes may be made from biological (human or animal origin) or synthetic materials. Temporary skin substitutes provide a physical barrier from bacteria and trauma and can create a moist physiological environment for wound healing. Permanent skin substitutes are meant to replace the components of skin and offer a higher quality of skin replacement. One of the oldest used skin substitutes is amnion, which is the innermost layer of the foetal membrane. It can be prepared in fresh, dried, frozen, freeze-dried irradiated, stabilized, or cryopreserved forms [73]. Patients’ epidermal cells are cultured and Cultured Epidermal Autografts (CEA) or artificial skin can be prepared. These can be used on wounds and burns for improved re-epithelization. Dermal substitutes from animal skin and animal collagen have also been used in the management of chronic non-healing wounds [74]. Acellular extracellular matrix scaffold derived from porcine jejunum submucosa fabricated as a dermal substitute has shown evidence of improved tissue regeneration and wound healing [75, 76].

Negative pressure wound therapy (NPWT)

NPWT is also called vacuum-assisted wound closure. The wound closure is facilitated by the continuous application of sub-atmospheric pressure to the wound area. Commercially available systems for negative pressure wound therapy (NPWT) include open-cell foam dressing put into the wound cavity and the vacuum-assisted closure (VAC therapy) device [77] (fig. 10).

NPWT systems consist of an open-pore polyurethane foam sponge that is placed over the wound. It is covered by a semi-occlusive dressing and then connected to a suction pump [78]. Once in position, the Negative Pressure dressing provides a stable environment over the wound surface. This enables the wound to heal even in the mobile patient without shear stresses affecting the wound, which could damage the fragile newly formed tissue. This method of treatment increases local blood flow and reduces edema and bacterial colonization rates. It is thought to promote closure of the wound by promoting the rapid formation of granulation tissue as well as by mechanical effects on the wound. It concurrently provides a moist wound environment and removes excess wound exudates, thus aiding in the creation of the "ideal wound healing environment" [79].

Hyperbaric oxygen therapy (HBOT)

Hyperbaric oxygen therapy (HBOT) is the use of 100% oxygen at pressures greater than atmospheric pressure. It has been successfully used as adjuvant therapy for the treatment of wounds. HBOT is administered to patients in pressurized chambers (fig. 11) with air or oxygen. The patient breathes oxygen intermittently. Hyperoxia causes vasoconstriction, angiogenesis, fibroblast proliferation, leukocyte oxidative killing, toxin inhibition, and antibiotic synergy [82, 83].

Futuristic approaches in wound care

Almost all of the currently existing wound dressing are passive and do not provide any information regarding the wound bed or the status of healing. Chronic non-healing wounds have been the focus of innovative products intended for wound management. Research in smart systems, devices with sensing, responding, or reporting functions or a combination of these are reported to address many of the challenges associated with wound healing, particularly for chronic wounds [85].
pH monitoring wounds dressings help in monitoring the wound status. Extremely high pH could be a sign of infections in the wound [86-88]. Temperature measurements at the wound site provide information about blood flow and angiogenesis and fibrosis. Temperature monitoring wound healing devices [89, 90, 95] can help in monitoring hypothermia. Dressings with oxygen sensors that can monitor tissue oxygenation can provide valuable data on wound healing [91, 92].

In addition to the above, dressings that can monitor moisture levels at the wound site, [93], and wound dress that can deliver drugs or healing factors at a rate and amount required by the healing wound [94, 95] are the more recent advances in this field.

Fig. 11: Hyperbaric oxygen chamber [84]

CONCLUSION

Wound healing rate and mechanism involve various interlinked and hence all wounds cannot be treated as same. All wounds heal differently. A deep understanding of various physiological and systemic factors is essential for appropriate wound management. With the availability of complex and advanced wound healing devices, it becomes increasingly more important for thorough systematic assessment of the wound and all systemic factors related to wound healing, so that these products can be used effectively with maximum impact. Knowledge about advanced wound healing techniques opens up new avenues in the designing of newer, better, and cost-effective treatment options.

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