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Emerging Technologies in Wound Care and Treatment, Strategies for Regeneration

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Abstract

The process of tissue regeneration in response to severe injury involves a complex mechanism known as wound healing. Diabetic and non-healing wounds pose a significant challenge in clinical practice. Presently, various treatment approaches are employed to address acute and chronic wounds, including tissue transplantation, cell therapy, wound dressings, and the use of medical devices. Extensive research has been conducted on this subject; however, finding the most effective clinical treatment remains a daunting task. Wound dressing entails the utilization of scaffolds, typically made of biomaterials, for the delivery of medication, autologous stem cells (SCs), or growth factors derived from blood. Antibacterial and anti-inflammatory drugs are also utilized to combat infection and expedite wound healing. Given the rising elderly population and the subsequent increase in diabetes and associated skin wounds, there is an urgent need to enhance current treatment strategies. This study critically evaluates the advancements in therapeutic and clinical approaches for wound healing and tissue regeneration. Recent clinical trials have shown that modern dressings and skin substitutes offer the easiest, most accessible, and cost-effective means of treating chronic wounds. Advances in materials science, such as the use of graphene as a 3D scaffold and biomolecules, hold great promise in this field. The annual market value for successful wound treatment exceeds $50 billion US dollars, which serves as a driving force for both industries and academia to explore the application of emerging smart materials in modern dressings and skin substitutes for wound therapy.

Keywords: Tissue regeneration, Scaffolds, Wound care, Stem cells

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Introduction

The skin functions as a barrier shielding us from the outside world and preventing microbial intrusion. When the skin is compromised, microorganisms can infiltrate the body, potentially causing infection. Severe skin damage can result in the loss of bodily fluids, electrolytes, and nutrients, posing a significant risk to life [1]. Wound formation is attributed to structural and functional disruptions in healthy skin, which can arise from various factors such as mechanical trauma, injury, diabetes, burns, heat-related harm, genetic disorders, or surgical procedures [2].

There exist various categories of injuries, and the methods of healing vary, relying on disorders, medical facilities, healthcare providers, and medical staff. The primary technique for treating wounds is through the application of wound dressings. In recent times, contemporary wound dressings have gained popularity and are frequently crafted in diverse forms to provide distinct characteristics. Additionally, due to challenges like diverse existing products, exorbitant expenses, and absence of standardized procedures, their practical applications are restricted or lack effectiveness. In this instance, evaluations are conducted on the findings of clinical trials, emphasizing encouraging results that demonstrate significant translation from laboratory to patient care [3-5].

Wound management expenses consist of supplies and bandages (15% - 20%), nursing hours (30% - 35%), and hospitalization (over 50%). Frequent dressing alterations augment the expenditure of wound care. Hence, the utilization of dressings that decrease the necessity for cleaning and removal of damaged tissue and exhibit greater clinical efficacy is of utmost importance [6, 7]. The objective of this investigation was to meticulously evaluate the present progress in the curative and clinical methods for the restoration of wounds and the regrowth of tissue. The aim of this study was to critically assess the current advancements in the therapeutic and clinical approaches for wound healing and tissue regeneration and to deliver instruction and clinical counsel.

The Process and Phases of Wound Healing

Wound healing is classified as primary, secondary, and tertiary wound healing (Figure 1).

Primary healing or primary intention

Uncomplicated healing of a non-infected, well-approximated wound is defined as primary healing. e.g., surgical wounds.

Secondary healing or secondary intention

If the wound healing course in this wound is disrupted by infection,

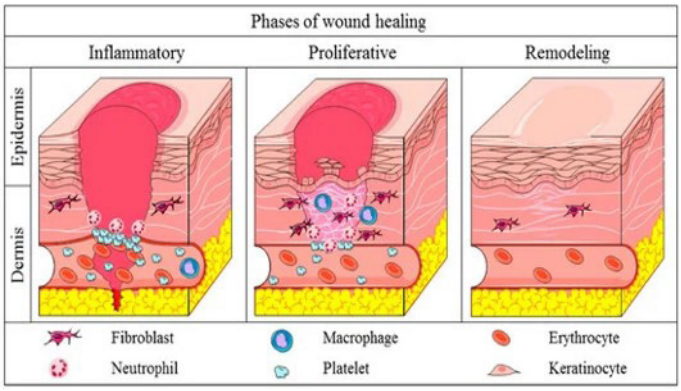

Figure 1: Phases of wound healing [11].

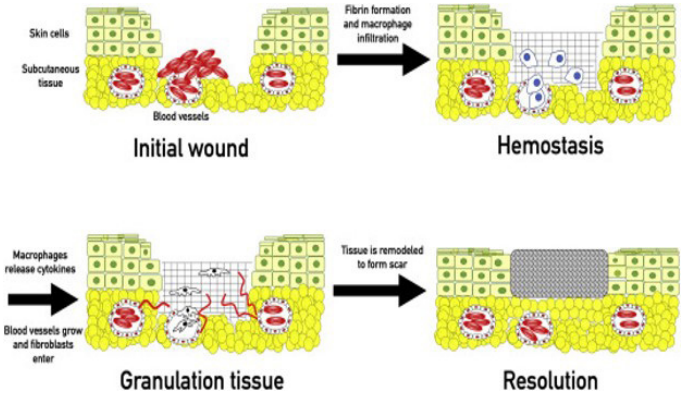

Figure 2: Physiology of wound healing [24].

dehiscence, hypoxia or immune dysfunction, the secondary healing stage begins. During secondary healing, granulation tissue formation and epithelization over this new tissue take place. These types of wounds are more susceptible to infections and poor healing [8].

Tertiary healing or third intention

It is delayed primary wound healing after 4 - 6 days. This occurs when the process of secondary intention is intentionally interrupted, and the wound is mechanically closed. This usually occurs after granulation tissue has formed. The interaction among cells, growth factors, and cytokines is vital in the wound healing process, resulting in the closure of the injury. This process can be categorized into four stages, each with its own explanation.

Wound Healing Stages in Adults

The initial stage is referred to as hemostasis, which involves initiating the coagulation cascade to prevent blood loss by creating a fibrin clot (Figure 2). The second stage is the inflammatory phase, which starts immediately after the injury and can persist for a maximum of 6 days [9]. Throughout this phase, immune cells at the wound site secrete proteolytic enzymes and pro-inflammatory cytokines, triggering the onset of inflammation. Inflammatory cells, especially in chronic wounds and burns, generate reactive oxygen species to hinder the entry of microorganisms and bacteria. Macrophages and neutrophils play a critical role in eliminating foreign particles and tissue debris during the inflammatory phase. The following phase is the proliferation phase, which begins 4 days after the injury and can potentially last up to 14 days. During this phase, re-epithelialization and the formation of granulation tissue take place, resulting in the development of the extracellular matrix (ECM). The final stage of wound healing is the

Table 1: Characteristics and uses of wound-dressing materials [13].

Category	Examples	Description	Applications
Alginate	AlgiSite, Comfeel, Curasorb, Kaltogel, Kaltostat, Sorbsan, Tegagel	Alginate dressings are made of seaweed extract contains guluronic and mannuronic acids that provide tensile strength and calcium and sodium alginates, which confer an absorptive capacity. Some can leave fibers in the wound if they are not thoroughly irrigated. These dressings are secured with secondary coverage.	These dressings are highly absorbent and useful for wounds that have copious exudate. Alginate rope is particularly useful to pack exudative wound cavities or sinus tracts.
Hydrofiber	Aquacel, Aquacel-Ag, Versiva	An absorptive textile fiber pad, hydrofiber is also available as a ribbon for packing deep wounds. This material is covered with a secondary dressing. The hydrofiber combines with wound exudate to produce a hydrophilic gel. Aquacel-Ag contains 1.2% ionic silver that has strong antimicrobial properties against many organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci.	Hydrofiber absorbent dressings used for exudative wounds.
Debriding agents	Hypergel (hypertonic saline gel), Santyl (collagenase), Accuzyme (papain urea)	Various products provide some chemical or enzymatic debridement.	Debriding agents are useful for necrotic wounds as an adjunct to surgical debridement.
Foam	LYOfoam, Spyrosorb, Allevyn	Polyurethane foam has absorptive capacity.	These dressings are useful for cleaning granulating wounds with minimal exudate.
Hydrocolloid	CombiDERM, Comfeel, DuoDerm CGF Extra Thin, Granuflex, Tegasorb	Hydrocolloid dressings are made of microgranular suspension of natural or synthetic polymers, such as gelatin or pectin, in an adhesive matrix. The granules change from a semihydrated state to a gel as the wound exudate is absorbed.	Hydrocolloid dressings are useful for dry necrotic wounds, wounds with minimal exudate and for clean granulating wounds.
Hydrogel	Aquasorb, DuoDerm, Intrasite Gel, Granugel, Normlgel, Nu-Gel, Purilon Gel, KY Jelly	Hydrogel dressings are water-based or glycerin-based semipermeable hydrophilic polymers; cooling properties may decrease wound pain. These gels can lose or absorb water depending upon the state of hydration of the wound. They are secured with secondary covering.	These dressings are useful for dry, sloughy, necrotic wounds (eschar).
Low-adherence dressing	Mepore, Skintact, Release	Low-adherence dressings are made of various materials designed to remove easily without damaging underlying skin.	These dressings are useful for acute minor wounds, such as skin tears, or as a final dressing for chronic wounds that have nearly healed.
Transparent film	OpSite, Skintact, Release, Tegaderm, Bioclusive	Transparent films are highly conformable acrylic adhesive films with no absorptive capacity and little hydrating ability. They may be vapor permeable or perforated.	These dressings are useful for clean, dry wounds with minimal exudate. They also are used to secure an underlying absorptive material, to protect high-friction areas and areas that are difficult to bandage (e.g., heels) and to secure intravenous catheters.

remodeling (maturation) phase, where type III collagen is substituted by type I, and the tensile strength of the newly formed tissue increases as the composition of the ECM changes [10, 11].

Methods in Treating Wounds

The process of wound healing is a complicated and multifaceted physiological phenomenon. Depending on the nature of the wound, various treatment approaches and techniques, encompassing a broad spectrum of expenses, have been employed [12]. These include swabbing to detect and combat infection, removing tissue debris from the wound bed, transplantation, cell therapy, application of wound dressings, and utilization of instrumental methods. This demonstrates that none of the methods utilized for wound treatment are flawless or completely efficient, thus rendering it an unresolved clinical necessity. In this study, we conducted a comprehensive examination of wound dressings and emerging technologies, such as regenerative medicine, for the purpose of wound healing [13]. Characteristics and uses of wound dressing materials are mentioned in the table below (Table 1). Additionally, we also mentioned other methodologies of treatment.

Transplantation of skin or SCs/cells

To regenerate tissue with this strategy, either skin or cells or SCs and their derivatives can be transplanted [14]. Skin transplantation is a crucial technique in reconstructive surgery for individuals who have experienced burns, injuries, and non-healing or sizable wounds. Mastering this technique is vital to enhance the well-being of patients with substantial wounds and extensive burns. This process examines the reasons for skin transplants, the preparation of the wound site, and the necessary stages to achieve a successful grafting of wounds. It elucidates the involvement of the interprofessional team in overseeing the healthcare of patients with burns and large or non-healing wounds (Figure 3). Figure 4 presents traditional wound dressing.

Cell therapy

In cases like burns, it is crucial to swiftly eliminate dead tissue and close the wound as quickly as possible. It becomes necessary to remove the affected area and replace it with healthy skin from other parts of the patient's body. However, this becomes challenging when there is a scarcity of unharmed skin in extensive burn cases [15]. To address this issue, a portion of the patient's own skin is isolated, and epidermal cells are cultured for several weeks before being applied to the damaged skin. This procedure is primarily performed in educational medical facilities and is not a routine practice due to the expertise and cost involved in cell proliferation, as well as the risk of infection. The cost of this method is quite high, amounting to $800 per 50 cm^2. Therefore, it is advisable to reserve this technique for patients with severe burns who lack sufficient

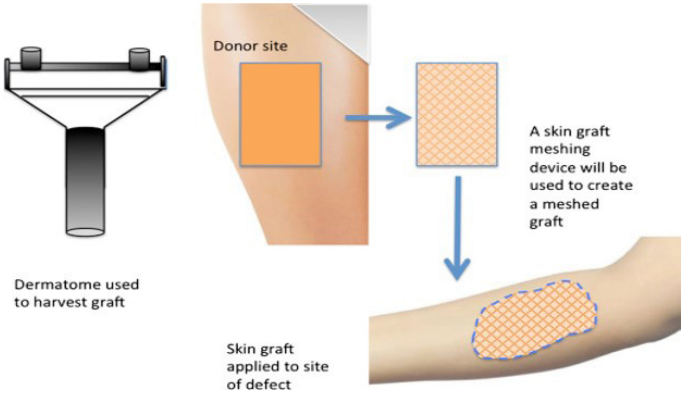

Figure 3: Harvesting and application of split skin graft [30].

Figure 4: Traditional wound dressing.

viable skin for autologous grafting [16-20].

An alternative approach involves utilizing "finely chopped micrograft" on the affected region. In this technique, a compact region of approximately 2 cm^2 of undamaged skin (epidermis and dermis) is acquired from the patient and subsequently fragmented into small fragments, blended with a hydrogel, and administered to the injured area. This is an economical and uncomplicated method that possesses the capability to replicate the skin's structure. Additionally, the technique of skin graft meshing serves as another treatment option. In this procedure, a small portion of the skin is extracted using a dermatome and positioned on the prepared wound area. The meshed grafts typically expand up to four times their original size. The lesser the degree of meshing, the greater the cell density, and the higher the likelihood of success. Furthermore, the larger the affected region, the lengthier the time required for wound closure, thereby increasing the risk of scarring [21].

As recent advances in wound management have demonstrated, autogenous keratinocytes and bioengineered skin substitutes can be cultured in vitro and used clinically [22]. Currently, surgeons use autologous keratinocyte sheets for repair, which are capable of performing a wide range of repairs, but the challenge is that it is so easy to separate the epidermis from the dermis that blistering may occur on the repair surface and disrupt the healing process [23-24].

Several clinical applications have involved the transfer of healthy cells in suspension form to wound beds or the transfer of cells cultured on matrixes [24]. This method does not require separation of the epidermis and dermis, so cell adhesion is ensured on the repair area. Infection risks and treatment costs are reduced due to a shorter repair time compared to the use of keratinocyte sheets.

Wound treatment has seen the emergence of a novel approach known as SCs. These SCs, harvested from either embryonic or adult tissue, have the remarkable ability to self-renew and ensure homeostasis. Their involvement in the wound healing process has proven to be highly effective, particularly in the treatment of burn wounds, diabetic wounds, and bedsores. Epidermal SCs, derived from various sources such as the hair follicle, isthmus, infundibulum, and interfollicular epidermis, are commonly used in wound treatment [25]. However, the precise mechanisms by which SCs regulate proliferation, differentiation, and migration during wound healing remain unclear. It is also uncertain whether this dynamic process of regeneration is sustained and what the proliferation rate of the cells will be as the healing progresses. Existing studies have shown that repair of the skin epidermis does not disrupt the cellular hierarchy of SCs and progenitors, nor does it affect the balance between renewal and differentiation time. Therefore, SCs are universally recognized for their attributes, including unlimited self-renewal capacity, longevity, participation in tissue repair, and maintenance of bodily homeostasis. SCs can play a crucial role in the healing process, based on their characteristics [2]. Over the past few years, researchers have extensively investigated the use of topical SCs for

expediting wound healing. Bone marrow SCs have demonstrated their ability to accelerate healing in various types of wounds, including burns, diabetic wounds, and bed sores. Despite the significant advantages of this approach, there are a few drawbacks to consider. Firstly, the ideal method for the release and delivery of SCs remains unknown. Secondly, there is no standardized quantity of SCs required for optimal wound healing. Lastly, the proper cultivation, expansion, and characterization of SCs in the laboratory can take up to 3 weeks to 1 month, resulting in a considerable delay in healing large wounds. Moving forward, the focus should be on enhancing rapid cell proliferation in vitro, maximizing the presence of resident progenitor cells in the wound bed, ensuring effective release, and optimizing grafting [26]. Since 2010, there has been a notable emphasis on utilizing adult SC-based therapy, particularly adipose mesenchymal SCs for chronic skin lesions. The preparation of adipose mesenchymal stem cells involves centrifugation, filtration, and fragmentation. However, there are limitations such as difficulty in expanding a sufficient number of cells for human use, adhering to good manufacturing practices, and ensuring the survival of expanded cells. Consequently, the clinical application of adipose mesenchymal stem cells has not received adequate attention.

Transplantation of skin

Due to the deficiency of keratinocytes, the process of healing deep skin wounds through epithelial repair is slow. Therefore, it is recommended to urgently consider the transplantation of autografts, allografts, or xenografts for the purpose of tissue regeneration, replacement, or repair. Autografts have been proposed as the standard treatment for severe burns, including premature wound debridement and incisions [27]. However, in cases of extensive burns, the use of autografts is not feasible due to limited accessibility and the potential for scarring resulting from the absence of dermis. In this procedure, a thin layer of skin, comprising the entire epidermis and a portion of the dermis (known as a split-thickness graft), is harvested from a donor area using a dermatome and then placed at the site of the wound [28, 29]. The effectiveness of autograft-based wound treatment is dependent on the thickness of the dermis: the thicker the dermis, the faster the wound heals, and the less scar formation occurs. Since the transplant involves using the patient's own tissue, there is no risk of rejection. Nevertheless, in cases where autografts are limited or unavailable, allograft transplantation is considered, where tissue from a donor is separated and transferred to the recipient [30].

An allograft is the transplantation of healthy tissue from either a living person or a deceased individual. This procedure has been in clinical practice since World War II. Deceased individuals, commonly referred to as cadavers, are typically used as the source of allografts. To facilitate this, cadavers are preserved by freezing in skin banks and can be utilized as tissue donors when necessary. Cadaveric skin is widely employed in the management of burn wounds in numerous burn centers worldwide. Additionally, skin grafts can also be obtained from living donors. However, a major drawback of allograft transplantation is its temporary nature, as it is susceptible to immunogenic rejection by the recipient's immune system and the potential transmission of viruses.

Xenografts are occasionally utilized as temporary biological dressings for wounds when autograft and allograft tissues are scarce or unavailable. In fact, xenografts expose foreign collagen to the wounds, thereby aiding in skin regeneration and can be particularly suitable for surgical wounds. Large-sized bovine or porcine xenografts are now accessible for use [31-33]. However, aside from the potential risk of rejection and immune response, there is also the possibility of cross-contamination with bovine spongiform encephalopathy or porcine endogenous retroviruses. Currently, there is no available solution for effective xenograft screening to detect the presence of these viruses, and they may even be cellularized xenografts. Some recent research has indicated that the introduction of skin xenografts in mice does not cause inflammation, while it does lead to an increase in macrophages and the induction of regenerative characteristics. Despite significant progress in skin harvesting and transplantation, the success of the outcome is dependent on the angiogenesis of the newly transplanted tissue and cell infiltration. If these processes do not occur, the transplant will ultimately fail [34-38].

Skin substitutes should possess the qualities of being safe for biological use, having dual functionality, demonstrating clinical effectiveness, being user-friendly, and offering cost-efficiency. Categorically, skin substitutes are classified as either temporary or permanent based on their duration of application. Utilizing an autograft alone is not feasible for extensive and deep burns; therefore, surgeons frequently opt for artificial skin substitutes. These substitutes have the ability to prevent fatality and, depending on their purpose, can also impact the visual aspect of the skin [39]. Even in instances of successful regeneration, the dermis, epidermis, sweat glands, and hair follicles may not fully recover, resulting in the patient's body lacking complete control over temperature and humidity. In such scenarios, it is advisable to regularly apply protective cream.

Platelet therapy

Although autologous platelet-rich plasma (PRP) has been suggested as an effective wound healing treatment, there is insufficient evidence that it is effective for acute and chronic wounds. In this study, we examined and explained in detail the effectiveness, synergy, and possible mechanisms of PRP-mediated wound repair [40].

Platelets, which are derived from bone marrow megakaryocytes, have a significant function in primary haemostasis, blood clotting, inflammation, and the healing of wounds. These blood components contain secretory organelles called alpha granules, which have the ability to release cytokines, growth factors, and ECM modulators. These substances can promote the revascularization of damaged tissue, stimulate the proliferation and differentiation of mesenchymal SCs into specific cell types, and induce the migration, proliferation, and activation of fibroblasts for connective tissue repair, thereby expediting the process of wound healing [41]. Apart from these functions, platelets also contribute to the immune response by releasing chemokines and cytokines that activate immune cells, and by producing microbicide proteins, including kinocidins, that protect against microbes.

Plasmoplasm is a large portion of the blood, in which platelets can be found. Platelet therapy offers a different perspective on wound treatment. In addition to playing a role in blood coagulation, platelets contain growth factors that promote homeostasis, fibrin clot formation, and tissue repair. A number of publications have been published regarding the use of PRP for chronic skin and soft tissue ulcerations, including periodontal and oral surgery, maxillofacial surgery, orthopedic and trauma surgery, cosmetic surgery, spinal surgery, heart bypass surgery, and burns [42].

The regeneration process is stimulated by platelet concentrates, which depends on the quantity and density of platelets, the type of leukocytes trapped in the fibrin network, and the release of active substances at the injury sites. Blood is centrifuged to prepare platelet concentrates, which can be either first generation concentrates like PRP and platelet-poor plasma, or second generation concentrates like platelet-rich fibrin (PRF), leukocyte-platelet-rich fibrin (L-PRF), and advanced platelet-rich fibrin (A-PRF), depending on the preparation protocol [43].

The PRP is a highly concentrated form of blood plasma that contains abundant platelets and growth factors. PRP has a higher platelet concentration compared to normal blood, with platelet therapy typically having a tenfold increase in platelets and growth factors. This higher concentration of growth factors in platelet therapy speeds up the healing process of wounds. PRP is usually obtained from the patient's own blood, making it a low-risk treatment option. It has been successfully used in clinical settings to heal both chronic and acute wounds. The presence of protein substances like cytokines and growth factors in PRP enhances the healing of various conditions such as diabetic foot ulcers, pilonidal sinus, maxillofacial surgeries, plastic surgeries, discogenic low back pain, and skin and soft tissue lesions. PRP promotes the regeneration of endothelial, epithelial, and epidermal tissues, as well as the formation of new blood vessels, synthesis of collagen, and repair of damaged tissues. The release of various growth factors commences with the breakdown of platelet α granules in PRP, which in turn speeds up the healing process of wounds [44]. PRP consists of seven distinct growth factors, namely platelet-derived growth factor (PDGFa and PDGFb), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), insulin-like growth factor (IGF), epidermal growth factor (EGF), and connective tissue growth factor (CTGF). Angiogenesis plays a crucial role in the wound healing process, with VEGF, abundantly present in PRP, being recognized as one of the most potent growth factors for promoting blood vessel formation and the production of factors like matrix metalloproteinases. During the homeostasis stage of wound healing, PRP plays a vital role. Specific platelet components in PRP include both anti-inflammatory and pro-inflammatory cytokines, which may contribute to the activation of wound repair mechanisms [2].

The PRP serves as a multi-antimicrobial ingredient that serves to prevent infection in wounds. Numerous investigations have demonstrated that PRP exhibits antibacterial properties against *Candida albicans*, *Cryptococcus neoformans*, *Escherichia coli*, and *Staphylococcus aureus* [46]. The PRP gel has also been shown to accelerate wound closure and granulation tissue formation in cutaneous leukocytoclastic vasculitis, which is another application of PRP. In general, using PRP can be a safe and cost-effective method for different wound healings, and it can reduce the time spent on treatment [2].

The PRF is actually the second generation of platelet-rich concentrates that are prepared by centrifuging blood in a tube. Because of their regenerative properties, platelet-rich concentrates have been considered in various fields of medicine in the past two decades.

The potential benefit of PRF as an autologous biologic additive is its ability to release growth factors over a long period of time. PRF consists primarily of platelets surrounded by fibrin filaments. PRF contains over 75% platelets. PRF can release various growth factors like PDGF, IGF, TGF-β, and VEGF, which have a strong impact on angiogenesis and accelerate the healing process of wounds. Additionally, PRF contains optimal levels of thrombin, which enhance angiogenesis by promoting the migration of endothelial cells and fibroblasts. Its distinctive fibrin structure not only traps blood SCs but also aids in cell adhesion and spreading [47]. The advantages of utilizing PRF include its affordability, lack of immune response stimulation, ability to speed up tissue repair, and simple one-step preparation. In contrast, direct injection of growth factors at a specific location in the body leads to their destruction and unstable diffusion, making their use more limited compared to PRF. Therefore, PRF offers a more sustainable release of growth factors, making it a promising option for treating chronic wounds such as diabetic foot ulcers and eye lesions.

Growth factors are present in abundance within PRP and contribute to accelerating the process of wound healing. Nevertheless, it has been observed that PRF is more effective in stimulating healing in comparison to PRP. The PRF also exhibits a longer duration of growth factor release in contrast to PRP [48-50].

Numerous establishments globally, particularly independent medical facilities, utilize blood derivatives like PRP and PRF for the management of wounds. Obtaining PRP from patient blood is a straightforward process and can be deemed non-intrusive. Nonetheless, its effectiveness remains uncertain. Multiple clinical experiments have been conducted, but none have involved multiple centers, and none have yielded definitive results. The precise mechanism by which these products facilitate wound healing is still not comprehensively comprehended. In certain instances, patients may have bleeding disorders or hematologic conditions that render them ineligible for this in-office treatment [2].

Characteristics and Types of Wound Dressing

Characteristics of an ideal wound dressing

The choice of dressing material should be based on the type of wound. The dressing should be able to: (a) create or sustain a moist environment, (b) facilitate the migration of skin cells, (c) encourage the growth of new blood vessels and connective tissue, (d) allow for gas exchange between the wound and the surroundings, (e) maintain an optimal tissue temperature to enhance blood flow and skin cell migration, (f) offer protection against bacterial infections, (g) be non-sticky and easy to remove once the wound has healed, (h) aid in the removal of dead tissue and support the movement of white blood cells, and (i) be sterile, non-toxic, and non-allergenic [51].

Types of Wound Dressing

Applying various types of wound dressings based on the characteristics of the wound, such as its type, depth, location, and size, is the most commonly used approach for treating wounds. Essentially, wound dressings act as a physical barrier that shields the wound from external factors, thereby safeguarding it against further harm and microbial invasion, ultimately expediting the healing process. The entry of microorganisms into the wound hampers and delays the healing process. Consequently, an ideal wound dressing should possess antibacterial properties to thwart wound infections and the development of bacterial biofilms [52, 53]. By employing an antibacterial wound dressing at the site of injury, the infiltration of bacteria and microorganisms can be prevented, thereby facilitating the natural healing process.

Wound dressings are typically categorized into three groups: (1) conventional, (2) non-active, and (3) contemporary wound dressings. Conventional wound dressings were utilized in ancient eras and were derived from tree leaves, plant extracts, spider webs, and honey. These materials were employed to prevent bleeding and isolate the wound from the external environment. Non-active dressings (such as sterile gauze, cotton pads, and bandages) merely cover the wound surface and absorb fluids, but they may adhere to the newly formed granulation tissue and cause discomfort upon removal. Nevertheless, despite the drawbacks, they are extensively utilized in clinical settings due to their effectiveness and simple manufacturing process [54].

Contemporary wound coverings comprise of sponges, membranes, gel-like substances, and gels with water content. These wound dressings can be composed of extremely compatible and organic substances like collagen, or artificial materials because of their increased strength and reduced expenses. Additionally, significant focus has been devoted to wound dressing containing cells and substances that promote growth,

like Apligraf (Organogenesis Inc., MA, US) derived from keratinocytes and fibroblasts found in human newborns. This two-layered skin replacement is the initial artificially created skin authorized by the US Food and Drug Administration [56].

Common materials used as wound healing constructs

Suitable wound dressings can be made using both artificial and organic polymers. However, natural biopolymers are more appealing for wound dressings due to their biocompatibility, biodegradability, biomimicry, and favorable physicochemical properties. These natural biopolymers have a structural resemblance to the ECM. When using biopolymer-based wound dressings, it is important to consider the degradation rate in relation to the wound healing process, as well as the release of active agents [57]. Additionally, the mechanical properties of the wound dressing should be taken into account, including tensile strength, elastic modulus, stiffness, stress stiffening effects, stress-relaxation rate, and viscoelasticity. These mechanical properties play a crucial role in wound dressing design as they can impact scar formation and stimulate the growth of fibrous tissue if the mechanical load transfer is not properly carried out. Tensile strength and flexibility are particularly important factors to consider when constructing wound dressings [58]. To prevent damage to underlying tissues, the wound dressing should be flexible with a low flexural modulus, while also possessing similar tensile properties to the skin. Natural polymers have been widely utilized in the development of commercial wound dressings [59].

Most of the research on wound healing conducted so far has been in a laboratory setting. Although some evaluations have been done on animal models, the number of clinical trials focusing on wound therapeutic approaches is relatively small [60].

The selection of treatment method depends on the type of wound, its severity, and the patient's medical condition. For instance, burn patients are categorized into grades 1, 2, and 3, each requiring different treatment priorities, either to save the patient's life or to alleviate pain [61-63]. In the case of cosmetic surgery, the focus is on promoting wound healing without any visible scarring, while for diabetic patients, preventing amputation is the top priority. Hence, the patient's condition plays a crucial role in determining the most suitable treatment option.

Wound dressings with incorporated biologics

Various growth factors and cytokines play a role in the different stages of wound healing, contributing to the progression of the wound from one phase to the next. The challenging environment within a non-healing wound often leads to a lack of cells that produce and release the necessary growth factors and cytokines, or the degradation of those that are present. Researchers have explored the use of biomaterials to deliver growth factors and cytokines to wounds, not only for wound healing but also for other regenerative purposes. This delivery requires the incorporation of the growth factors and cytokines into the biomaterials, as well as their transportation to the specific site of action in an active and functional state and at an appropriate concentration. As previously mentioned, within the body, many growth factors are bound and protected by heparin/heparan sulfate, including certain fibroblast growth factors and members of the VEGF family, as well as various cytokines associated with inflammation. To mimic these interactions, heparin has been added to wound healing therapeutics to safeguard and deliver growth factors, such as VEGF and TGF-β. Other approaches to incorporate growth factors include covalent integration or genetically modified proteins to include the desired growth factors. Additionally, growth factor fusion proteins produced through recombinant expression can be integrated into biomaterial scaffolds for wound healing therapies [57]. Furthermore, the addition of exogenous growth factors or cytokines into biomaterial scaffolds has been shown to stimulate the expression of endogenous growth factors.

Nanomaterials

Nowadays, the extensive application of nanomaterials is primarily attributed to their distinct characteristics, which include a remarkably vast specific surface area and elevated surface energy. Generally, nanomaterials are capable of actively contributing to various aspects of the wound healing process, including haemostasis, inflammation regulation, cell proliferation, and antimicrobial activity. Among the numerous materials utilized in wound dressings to combat bacterial infections and expedite wound healing, metal nanoparticles such as silver, gold, and zinc have been widely employed. Additionally, the utilization of liposomes, mesoporous silica, and drug-loaded nanomaterials has exhibited promising outcomes in numerous studies. More recently, carbon nanomaterials like carbon nanotubes, graphene, and graphene oxide (GO) with distinctive physicochemical properties have been explored for their potential applications in modern wound dressings, which will be briefly discussed in the following section [64, 65].

The remarkable characteristics of carbon nanotubes (CNT), such as their superior electrical conductivity, mechanical strength, and lightweight nature, have greatly broadened their utilization in the creation of scaffolds for tissue engineering. So far, CNT-infused nanomaterials have been extensively researched for their potential applications in various fields including biomedicine, biosensors, drug transportation, tissue engineering, and wound healing [66]. Modified CNT, known for its extensive surface area, has gained significant popularity as a nanocarrier for efficient drug delivery. Moreover, CNT has the ability to eradicate or inhibit the growth of bacteria [67]. CNT-based dressings have been proven to enhance the migration and multiplication of fibroblast cells, while also exhibiting a noteworthy impact on the potential for angiogenesis.

Graphene and GO

Graphene, which has a 2D structure, is an alternative form of carbon that has been suggested as a novel carbon nanomaterial for tissue engineering. Its unique characteristics encompass outstanding mechanical strength, high thermal and electrical conductivity, and biocompatibility. GO, a graphene-based material, exhibits reduced thermal and electrical conductivity compared to graphene due to the incorporation of oxygen groups and structural modifications [68]. The presence of carboxyl, hydroxyl, and carbonyl groups on GO enables its interaction with various materials, including polymers. Consequently, many bioengineering researchers have transitioned towards the utilization of GO instead of graphene.

The general purmoisture and dressings containing graphene-based nanomaterials is to promote cell proliferation, adhesion, differentiation, and growth, as well as increase mechanical properties, preserve wound moisture, and improve biocompatibility [2]. As a drug carrier, graphene-based nanomaterials have also been used in various studies, either alone or in combination with biopolymers.

Limitations of nanoparticles in wound healing

Nanoparticles (NPs) possess an admirable ability to promote wound healing, and there are still significant opportunities for their utilization and advancement in the future. However, it is important to note that the wound surface is not protected by intact skin. NPs, when used in wound healing, come into direct contact with the tissue, making the biological safety of the NPs crucial prior to application. The

commonly reported adverse effects of NPs on the skin include irritation and allergies. For example, carbon nanotubes and nickel NPs have been found to induce skin hypersensitivity due to the release of ions and surface coatings from the NPs. Studies have shown that transdermal exposure to NPs can worsen skin inflammation, irritation, and psoriasis. Additionally, exposure to NPs has been associated with oxidative stress, autophagy, and programmed cell death in fibroblasts and keratinocytes. The toxicity of NPs (such as nickel, gold, and silver) depends on factors such as shape, size, surface charge, stability, and concentration. Therefore, when developing novel NPs for wound treatment, it is crucial to modify their physicochemical properties in order to reduce their harmful effects on skin cells. Enhancing NP stability can help decrease NP-induced dermatitis. Stabilizers, such as metal shells, polymers, or surfactants, can be employed [69].

Moreover, it is crucial to utilize materials with low sensitization for coating the surface of NPs in order to minimize skin irritation. Furthermore, it has been reported that NPs induce DNA damage and diminish gene methylation, indicating the potential for cell canceration. However, there is no definitive evidence to support the notion that NPs can cause malignant alterations and hereditary gene mutations in skin cells. Additionally, there is insufficient proof to suggest that prolonged exposure of NPs to the skin, resulting in percutaneous absorption and deposition, will have significant impacts. It is imperative to conduct extensive exposure studies in the future to establish this. Once NPs enter the body, they come into direct contact with blood cells through damaged blood vessels in lesions, leading to hemolysis. Some metal NPs, like AgNPs and ZnO NPs, have been demonstrated to induce hemolysis. To address this complication, the physicochemical properties of the material can be modified, or the surface of NPs can be coated with biologically active substances, such as polysaccharides and phospholipids.

A different concern arises when NPs disperse throughout the body and affect various organs, resulting in multiple system impairments. The concentration of NPs in the bloodstream significantly decreases compared to the initial concentration, and a portion may be excreted through urine and feces. Animal studies have shown weight loss and mortality, but there is insufficient evidence to determine whether NPs can cause organ damage and/or tumors in practical applications [69]. Furthermore, introducing NPs during pregnancy can disrupt the development of offspring. Evaluation of NP toxicity in wound healing has mainly focused on local acute adverse reactions. On the other hand, research on metal NPs, carbonaceous NPs, and nanotubes has been more prevalent, while nanofibers, nanofilms, and other innovative NPs have received limited attention. Therefore, it is crucial to conduct immediate investigations into NP toxicity to address these complexities.

Instrumental Method

Below is a short summary of instrumental methodology used to treat wounds.

Negative pressure wound therapy

The negative pressure wound therapy (NPWT) system consists of three main parts: a sponge, a semi-occlusive barrier, and a fluid collection system that exerts uniform negative pressure on the wound surface (Figure 5) [70]. By improving local blood flow, causing macro deformation, promoting granulation, promoting angiogenesis, reducing oedema, and reducing bacterial colonization, this method accelerates wound healing.

Fluid removal is utilized by the NPWT to regulate the exudate, thereby preventing infection and cross-contamination. This approach also reduces swelling, stimulates the formation of new blood vessels, aids in maintaining the moisture of the wound, and ultimately facilitates the contraction of the wound edges [71]. This method has been employed in the treatment of both acute and chronic wounds, as well as open wounds, burns, diabetic wounds, and venous and arterial wounds.

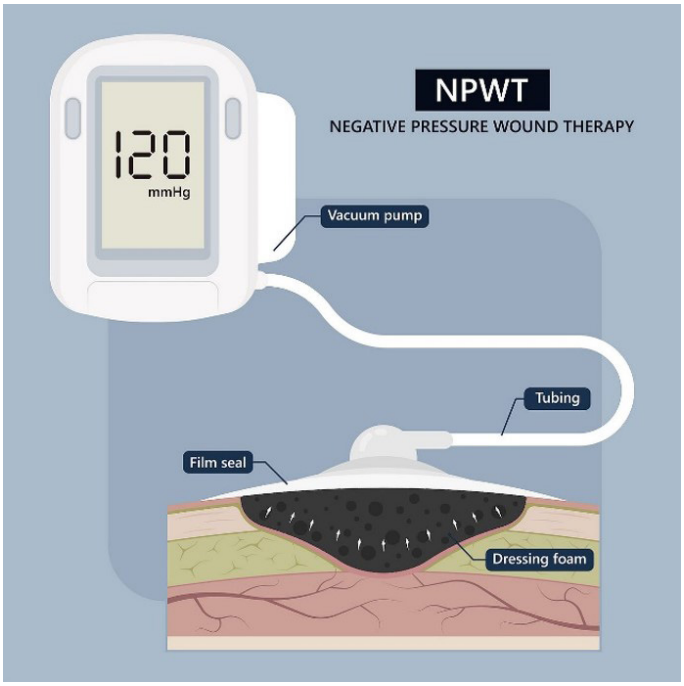

Figure 5: Miniature diaphragm pump used in NPWT [72].

In general, despite the fact that numerous patients have undergone NPWT treatment, including those at our own institution (Royal Free Hospital, London), there is no conclusive evidence to suggest that NPWT is significantly superior to conventional therapy. While some clinical trials have been conducted, they have not yielded definitive results. As a result, a well-organized, multicenter clinical trial is necessary to verify the efficacy of NPWT as a wound healing tool.

Hyperbaric oxygen therapy

The role of oxygen in the healing process of chronic wounds is significant. Hyperbaric oxygen therapy (HOT) involves the administration of 100% pure oxygen in a closed chamber with a pressure approximately three times higher than normal atmospheric pressure. This method is non-invasive and relatively safe. HOT has been shown to bring about beneficial physiological changes, including increased angiogenesis, improved collagen deposition, activation of leukocytes, and reduction of edema. However, a comprehensive clinical study involving 6259 patients who received hyperbaric oxygen treatment concluded that it did not enhance wound healing or prevent amputation. Perren et al utilized the HOT technique to treat Ischaemic Foot Ulcers in individuals with Type 2 Diabetes [73]. Their findings indicated that the HOT treatment improved the area and depth of the ulcers compared to the control group. Lansdorp et al conducted a study on the effect of HOT on perianal fistulas in patients with Crohn's disease, and significant improvements were observed in clinical, radiological, and biochemical aspects among those in the treatment group.

Low-level laser therapy

Low-level laser therapy (LLLT), a form of phototherapeutic treatment, utilizes various gas components (Figure 6). The commonly used LLLTs include helium/neon, aluminum/gallium/indium/

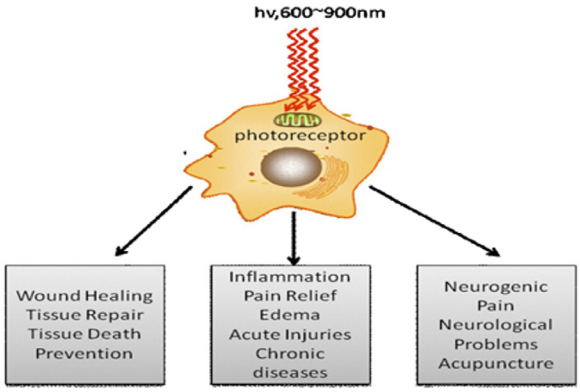

Figure 6: Schematic representation of the main applications of LLLT [74].

phosphide, gallium/aluminum/arsenide, and gallium/arsenide, each with distinct wavelengths for targeting different tissue depths. Besides wavelength, important parameters in LLLT include power, pulse rate, pulse duration, interpulse interval, total irradiation time, intensity (power/area), and dose (power irradiation time/area irradiated). The primary action mechanism of this laser type is photothermal effects, although it typically does not induce significant temperature changes [2].

The specific mechanism of this technique remains unknown, but it appears that the method reduces inflammation of wounds by decreasing the production of chemicals by cells and inhibiting pain and inflammation-related enzymes. The key factors influencing the effectiveness of this approach include the optimal wavelength, dosage of radiation, treatment duration, and treatment location. The LLLT application has been found to be effective in treating acute, chronic, and postoperative wounds. Clinical trials utilizing LLLT for wound healing have shown positive results, although there have also been clinical studies indicating that the use of LLLT does not significantly enhance wound healing.

To summarize, these three methodologies are intriguing and have demonstrated some improvement in wound healing when applied [74, 75]. However, none of them have shown significant improvements that would warrant replacing the current treatment approach. These methodologies have primarily been utilized in university hospitals and by clinical researchers, and their implementation in general hospital clinical settings has not been fully realized.

Cold atmospheric pressure plasma

Cold atmospheric pressure plasma (CAP) is a wound treatment technique that works by deactivating harmful microorganisms and promoting tissue regrowth. This type of plasma is typically created in specialized low-pressure reactors (with a pressure below 133 mbar) using various methods like direct current, radiofrequency, microwave, or pulsed discharge systems. The exact mechanism by which plasma aids in wound healing is not fully understood. However, the sterilizing properties of reactive oxygen and nitrogen species produced by cold plasma may play a role in expediting the healing process. These reactive species are known to influence cellular responses, including cell differentiation, apoptosis, and acting as second messengers for treated cells [75]. By facilitating cell-to-cell communication, these signaling events are involved in different stages of wound healing, including the acceleration of re-epithelialization. Studies have demonstrated that CAP promotes the growth of fibroblasts, endothelial cells, and epithelial cells, as well as activating the integrin of fibroblasts and epithelial cells. These effects are comparable to the activity of nitric oxide and reactive oxygen species during the natural wound healing process. The application of the CAP method has been extensively researched for its potential in treating various types of wounds, such as diabetic foot ulcers, herpes zoster, psoriasis, and warts. Clinical results have confirmed the accelerated wound healing achieved through this method [65].

Future Prospectus

Presently, addressing the issue of wound treatment, including those related to diabetes, is recognized as a clinical requirement that has yet to be fulfilled. As a result, substantial financial resources have been invested worldwide in the pursuit of an improved treatment option. This review highlights various treatment methods, some of which have displayed promising outcomes, particularly the utilization of bioactive wound dressings [66]. While the techniques employed in instrumentation are intriguing, clinical trials have not yielded significant improvements, thus necessitating further advancement. Nonetheless, many wound treatments still remain unfulfilled clinical needs, demanding a multidisciplinary approach to the development of effective treatments. Recent clinical trials indicate that the use of modern dressings and skin substitutes represents the simplest, most accessible, and cost-effective approach for managing chronic wounds. Consequently, the ultimate objective is to produce a readily available and highly sought-after wound dressing that can be used as needed. In addition to the aforementioned, emerging technologies like 3D printing for personalization hold promise for the future [67, 76]. There has been a significant advancement in the development of advanced materials across various industries, including the medical field. The combination of innovative smart biomaterials, antibacterial medications, and nanoparticles, along with the potential use of SCs/cells extracted from patients in the clinic, such as blood products or adipose SCs/cells obtained through simple extraction, may offer a solution for wound treatment [70, 71]. Therefore, an interdisciplinary approach involving clinicians, scientists specializing in materials and biology, as well as engineers, is necessary to develop SC-based therapies or drug delivery systems that can provide more effective and safer treatment options for chronic wounds in the coming years.

Conclusion

The process of wound healing is a complex series of events that initiates with injury and leads to the creation of granular tissue and regeneration of skin, ultimately resulting in wound closure. Depending on the nature of the wound, the duration of treatment can vary, and in the worst-case scenario, there may be no response to treatment leading to the possibility of amputation. As emphasized in the evaluation, there are numerous treatment methods available, however, none of them guarantee 100% success. Consequently, the treatment of wounds is still considered an unfulfilled clinical requirement, and both academia and industries are actively exploring superior techniques. Currently, there is extensive research being conducted on growth factors and cytokines that are released from platelets and leukocytes, as they have a substantial impact on cellular functions like migration, differentiation, and proliferation, allowing them to regulate the wound healing process. Wound dressings are the most accessible and cost-effective means of wound treatment and are tailored to suit the type and location of the wound. An ideal wound dressing should possess antibacterial properties, be biocompatible, non-toxic, stable, hydrophilic, and capable of swelling. A comprehensive understanding of the wound healing process, combined with the integration of smart materials such as scaffolds, controlled drug release, and the incorporation of growth factors and cells, holds promise for advancing wound treatment. The effective treatment of wounds has garnered immense interest from pharmaceutical and medical device companies, leading to intense competition in this multi-billion-dollar industry.

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None.

Conflict of Interest

None.

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