Hydrogel Wound Healing: An Update

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➢ ABSTRACT

In the biomedical industry, hydrogels are frequently used and show promise. Hydrogel dressings' anti-inflammatory properties have been greatly enhanced in recent years, resolving numerous clinical issues that have arisen in continuous attempts to encourage wound healing. The process of wound healing is intricate and cascaded, particularly in chronic wounds like severe burns and diabetic wounds, where unfavourable endogenous or external variables can impede the healing process by interfering with the regulation of inflammation. Excessive inflammatory infiltration is a nearly universal characteristic of chronic wounds, despite the rarity of minimal wound inflammation. This prevents the lesion from healing histologically in a predictable biological step and chronological order. As a result, reducing excessive inflammation. Over the last five years, a great deal of study has is Research has been done on hydrogel dressings to treat excessive inflammation in wound healing. Specifically, these dressings effectively scavenge excessive free radicals, sequester chemokines, and promote M1- to-M2 polarization of macrophages, all of which help to control inflammation and promote wound healing. In order to promote healing, we presented new anti-inflammatory hydrogel dressings in this study and provided creative preparation and application techniques. We also go over our analysis of potential issues that have not yet been resolved and provide a summary of the most crucial characteristics needed for wound healing. crucial for wound healing.

1. INTRODUCTION

Being the largest organ in the body, the skin's main job is to protect the body from the weather. Numerous reasons, including pressure, venous stasis, thermal injury, trauma, and chronic ulcerations brought on by diabetes mellitus, can create a wound, which is defined as an injury or breakdown of skin tissue [1]. The body's first line of protection against the weather, dehydration, chemical or radioactive damage, and microbial invasion is the skin, which makes up the outer layer. A wound is any damage to the layers of skin that alters the structure and function of the skin. The moment a

wound is sustained, the healing process starts. Wounding occurs when the epidermal layer of the skin ruptures, exposing the dermis beneath to the air. Depending on the location and severity of the skin damage, blood vessels to bone are among the tissues exposed to the air [3]. Thus, wounds are usually classified into three categories. A cut is considered superficial if it just affects the surface of the epidermis. A wound that affects deeper skin layers, including sweat glands, hair follicles, and blood vessels, is said to be partialthickness. This happens when a full-thickness cut ruptures the deeper tissues or underlying subcutaneous fat. Burn injuries can be classified as first-, second-, or third-degree depending on the extent of the superficial, partial, and complete thickness of the wounds. Fourth-degree burns damage the muscles, tendons, and underlying tissues. ligaments, as well as bone. Additionally, they result in a loss of sensation in the affected area and a rupture of the nerve endings [4]. Wounds can result from a variety of causes, including trauma, surgery, external factors (such as pressure, burns, and cuts), and illnesses like diabetes or vascular diseases. Whether these damage types are classified as acute or chronic wounds depends on their underlying causes and consequences.

1.1 SKIN

The biggest organ in the human body is the skin. The external environment is continuously attacking the skin, which is the outermost barrier of our body [1]. The epidermis, dermis, and hypodermis are the three interrelated layers of the skin, and they are organized sequentially from the outermost to the interior layer [2]. Skin has several functions. It protects the skin from several forms of harm, including UV rays, and serves as a barrier against infection and water loss. thermal radiation as well as chemical radiation [3]. The epidermis, the skin's outermost layer, serves as a waterproof barrier and affects skin tone. The dermis, which lies beneath the epidermis, is connected to connective tissue, sweat glands, blood vessels, lymphatic vessels, and hair follicles. The hypodermis, the deeper subcutaneous layer, is composed of fat and connective tissue [4].

❖ The body is shielded by the skin from:

• Pathogens: Bacteria, microbes, and other dangerous substances are kept at bay by the skin's barrier function.

• UV light: Melanocytes, the pigment cells in the skin, provide protection from UV rays.

• Trauma: The skin shields the body from mechanical harm.

❖ The skin is composed of three layers of tissue:

➢ the outermost layer, the epidermis.

➢ The middle layer is called dermis.

➢ The lowest or fatty layer is called the hypodermis.

1.2 FUNCTION OF SKIN

• **Protection: -** As the body's first physical barrier against the outside world, the skin protects against pathogens, dehydration, UV light, and mechanical injury.

• **Regulation of Temperature: -**By absorbing or releasing heat, skin contributes to thermal control and supports the body's water and homeostatic balance.

• **Sensation of pain: -** The skin is the first organ to sense pain, warmth, touch, and deep pressure.

• **Mobility: -** The skin causes the body to move smoothly and gently.

• **Immunity: -**development of immunity against pathogens

• **Endocrine activity: -** The skin starts the metabolic reactions that produce vitamin D, which is necessary for a healthy metabolism of bones and calcium absorption.

• **Exocrine activity: -** The discharge of ammonia, urea, and water is known as exocrine activity. Skin produces bioactive chemicals like cytokines, which provide vital immunologic functions, as well as materials like sweat, sebum, and pheromones

1.3 SKIN STRUCTURE

Nearly 1.8 m² of skin are covered, and the skin weighs about 6%, or 1/16th, of the body weight (292). The epidermis's main function is to protect and shield the internal organs from moisture. It covers nearly the entire body and varies in thickness from 600 to 900 μ m on the soles to 5 to 50 μ m on the scrotum and eyelids [1]. In essence, the skin is made up of three layers. Subcutaneous tissue is the third and. The dermis, which lies beneath the epidermis, is connected to connective tissue, [2].95% of the epidermis is made up of keratinocytes, or epithelial cells that synthesize keratin, whereas the remaining 5% is made up of non-keratinocytes, or cells that do not synthesize keratin. A clear comparison between the various cell layers of the epidermis is made possible by the keratinocytes' changing cellular contents as they travel peripherally [3]. Thick skin sections such as the palms and soles are composed of the stratum corneum, stratum lucidum, stratum spinosum, stratum granulosum, and stratum basale the five layers of the epidermis. Because the epidermis only has four layers in some places, the stratum lucidum is absent. The second layer of the dermis is called the reticular dermis, and the first layer is called the papillary dermis. [4].

2. SKIN WOUND HEALING

The complex process of skin wound healing necessitates the interaction of multiple cell types and mediators within a complex time frame. In addition to giving new and recent knowledge, the following update on skin wound healing attempts to give the reader a brief overview of each stage [1]. A remarkable and unique cellular function mechanism is demonstrated by the healing of a skin wound. One aspect of the repair process is the intricate interplay between the cells, growth factors, and cytokines that coat the site of injury.

There are four primary stages in the predictable healing process of skin wounds:

• Inflammatory:

➢ White blood cells eliminate bacteria, platelets clump together to create a clot, and blood arteries constrict to stop blood loss. The wound could hurt, swell, and turn red.

➢ starts immediately following the injury when transudate—a mixture of water, salt, and protein—leaks from the damaged blood vessels, resulting in regional swelling.

➢ Inflammation inhibits infection and regulates bleeding.

➢ The fluid engorgement facilitates the migration of healing and repair cells to the wound site.

➢ Damaged cells, germs, and pathogens are eliminated from the wound site during the inflammatory phase.

• Maturation:

➢ It may take months or years for the body to finish refining the wound and adding collagen.

➢ The wound completely heals, and type III collagen is transformed into type I collagen.

➢Apoptosis, or programmed cell death, eliminates the cells that were used to heal the wound but are no longer required.

➢ The wound is thick and the collagen that was put down during the proliferative phase is haphazard.

➢ The tensile strength of the healing tissues is increased as a result of collagen remodel into a more ordered structure along stress lines. Matrix metalloproteinases are secreted by fibroblasts. Type III collagen can be remodel into type I collagen with the help of the enzymes.

• Haemostasis Phase

➢ Happens very quickly.

➢ Starts when blood leaks out of the body, then blood vessels constrict to restrict the blood flow.

➢ The platelets aggregate and adhere to the sub-endothelium surface within seconds of the rupture of a blood vessel's epithelial wall.

➢ After that, the first fibrin strands begin to adhere in about sixty seconds.

➢ As the fibrin mesh begins, the blood is transformed from liquid to gel through procoagulants and the release of prothrombin.

➢ The formation of a thrombus or clot keeps the platelets and blood cells trapped in the wound area.

• Proliferative Phase

➢ The wound contracts as new tissues are built.

➢ A new network of blood vessels must be constructed so that the granulation tissue can be healthy and receive sufficient oxygen and nutrients.

➢ Myofibroblasts cause the wound to contract by gripping the wound edges and pulling them together using a mechanism similar to that of smooth muscle cells.

➢ In healthy stages of wound healing, granulation tissue is pink or red and uneven in texture. Healthy granulation tissue does not bleed easily.

➢ Dark granulation tissue can be a sign of infection, ischemia, or poor perfusion.

3. WOUND HEALING

A wound is defined as a break in the continuity of the skin or mucosa caused by an internal or external damage, an underlying medical condition, or both [1]. The biological process of wound healing seeks to restore skin integrity while repairing damaged tissue [2]. Skin wounds are quite common in human life and present a significant difficulty in providing medical care. Depending on the duration of healing Depending on how long it takes for a wound to heal, it can be categorized as either acute or chronic. Cuts, scrapes, heat, and surgical incisions are just a few of the causes of acute wounds. In healthy people, these wounds typically heal fast and don't require medical care [3]. The four overlapping phases of wound healing—inflammation, homeostasis (blood clotting), proliferation (tissue development), and maturation (tissue remodeling)—are dynamic and multifaceted [4]. In the hemostasis stage, platelets clump together to form a platelet plug around injured blood vessel walls, while fibrin forms a clot in the blood at the wound site. The inflammatory stage is brought on by growth factors produced by platelets, during which neutrophils and macrophages combat microbes and break down necrotic tissue. The process of proliferation, which leads to total wound closure, includes the generation of epithelial cells, granulation tissue formation, neovascularization, and extracellular matrix (ECM) deposition.

3.1 TYPES OF WOUND HEALING

. Chronic Wounds

A chronic wound is one that has lost the integrity of one or more layers of the subsurface components and does not heal after 8weeks. Curing chronic wounds presents significant health challenges for people and the healthcare system [1]. Chronic wounds are those that result from metabolic issues. These wounds take a long time to heal in a balanced length of time, in contrast to acute wounds, which heal quickly. The disintegration of cells and extracellular matrix (ECM) is insufficient in chronic wounds. These wounds are frequently categorized into three groups: venous/vascular ulcers, diabetic ulcers, and pressure ulcers. [2] Ischemic ulcers. If a wound does not heal in a quick and

orderly fashion, or if the healing process is unable to restore the wound's physical and functional stability after three months, the wound is considered chronic.

. Vascular Ulcers

Hypertension or chronic venous insufficiency can cause venous ulcers. Exercise helps lower pressure in a healthy venous system by activating the calf muscle pump. The valves that link the superficial veins to the deep venous circulation stop backflow, or reflux, and keep the pressure low when muscles relax. Venous pressure stays high in systems with ineffective valves, though. About 0.7% of diabetic individuals with venous ulcers have an ABI of ≲0.8.26. In addition, venous insufficiency affects 13.97% of diabetic patients.34 Diabetes increases the chance of developing and worsening chronic venous illness, which can lead to venous ulcers as a consequence. A common pathophysiology involving hemodynamic abnormalities in the lower limbs, including vascular wall remodel.

. Diabetic Ulcers

One interesting aspect of diabetic ulcers is diabetic bullae. It is well known that diabetic skin problems have a variety of underlying causes, and numerous studies have looked at diabetic bullae. The underlying ethology of diabetic bullae, or blister formation, is unknown in about 39.7% of diabetic patients. Blisters frequently appear after mild trauma or UV radiation

exposure.36 Microangiopathy, immune-mediated vasculitis, poor metabolism of calcium, magnesium, or carbohydrates, tissue hypoxia, or microcirculation ischemia are some of the possible causes of diabetic bullae.29, 30 Patients with an ABI < 0.8 (1.07%) may have diabetic bullae due to microangiopathy.

• Pressure Ulcers

An open ulcer or intact skin are examples of pressure injury, which is a localized damage to the skin or subcutaneous soft tissue that may be accompanied by pain. It typically happens where the medical equipment is compressed or where the bone is prominent (Webb, 2017). Patients who are unable to shift positions frequently sustain stress injuries (Pancorbo-Hidalgo et al., 2006; Pieper et al., 2009). One preventive measure used in these situations is the administration of dressings; however, this method also raises the overall cost of care. Consequently, it is imperative to ascertain whether the application of these dressings offers patients any potential advantages (Sebern, 1986).

. Ischemic Wound

An ischemia wound, sometimes referred to as an arterial ulcer or ischemic ulcer, is a chronic wound that develops when a part of the body has decreased blood supply. Less frequently, Numerous circulatory-related diseases can result in ischemic wounds, including.

3.1.2 Acute Wounds

The complicated process of wound healing can be broadly broken down into three overlapping phases: remodeling, proliferation, and inflammatory response. In addition to vascular reactions like blood coagulation and hemostasis, the inflammatory phase also includes cellular processes including leukocyte infiltration with a variety of antimicrobial and cytokinereleasing roles, which starts the proliferative response for wound healing. In order to emphasize the significance of vascular responses, some authors have separated wound healing into four stages, with hemostasis as the first stage. During the proliferative phase, granulation tissue grows to fill the wound space while the epithelium forms to cover the wound surface. Fibroblast proliferation, collagen and other extracellular matrix deposition, and the growth of new blood vessels are all processes involved in the production of granulation tissue.

. Abrasion Or Scrapes

A scrape on your skin is called an abrasion. When your skin rubs off, a break occurs in your skin. It might hurt and bleed a little. When anything strikes or pulls against your skin, friction, an abrasion frequently results. Most often, abrasions are unintentional wounds. They only have an impact on your skin's outermost layers

. Avulsion Or Contusions

All layers of skin are affected by an avulsion injury. The tissue may be separated from the body, or you may be able to lift up a flap of tissue that is still attached. Sometimes the avulsed tissue can be healed if it is accessible and sufficiently healthy.2.

. Crush Or Cut Wounds

When a body part is subjected to excessive force or pressure, a crush injury results. The most common cause of this kind of damage is when a bodily component is squashed between two heavy objects.

➢ Crush injury-related damages include:

➢ Bruising that is bleeding Compartment syndrome is characterized by elevated pressure, typically, in the arm or leg, which results in significant damage to the muscles, nerves, blood vessels, and tissue.

. Lacerations

A skin wound that has no lost skin is called a laceration wound. Sharp things are typically the source of lacerations. These are among the simplest medical disorders to identify and manage. Tearing the soft bodily tissue, or the outermost layer or layers of skin, results in lacerations. Moreover, lacerations are atypical, tear-like wounds that are frequently brought on by blunt trauma.

. Missile Or Velocity Wounds

When a missile enters a live body, the kinetic energy (KE) that the projectile releases is absorbed by the tissue, causing injury. This energy transfer depends on the formula KE=3-MV2 and s connected to the missile's mass (M) and velocity (V). The most crucial element in the case of small-mass missiles, like bullets, is the missile velocity. Because of aerodynamic forces that lead it to deviate from the path of flight and increase the angular deviation of its longitudinal axis, a non-spinning bullet is unstable and tumbles, which, once initiated, continues.

. Radiation Wounds or Ulcers

A late-stage cutaneous reaction following radiation therapy for cancer treatment is radiation-induced ulcers. The current study looked at the potential of managing radiation-related wounds with a single-stage reconstructive technique. Thirty individuals who had radiation therapy for hemangiomas or cancer were enrolled in this prospective study. The patients were between the ages of 15 and 80. From October 2013.

4. HYDROGEL WOUND

Hydrogels show promise as a wound therapy since they can:

• **Improve the wound environment:** Hydrogels help wounds stay wet, which promotes healing and cell migration.

• **Reduce pain:** Hydrogels have the ability to cool and soothe the skin, which is beneficial for burns and other painful wounds.

• **Fight infection:** Hydrogels can aid in the treatment and prevention of infections.

• **Deliver drugs:** Hydrogels have the ability to transport and release medications, proteins, and cells straight to the wound.

• **Degrade slough:** Hydrogels have the ability to break down slough on the surface of wounds.

➢ **The following hydrogel varieties are used to promote wound healing:**

• Hydrogels based on chitosan

These hydrogels offer antibacterial, non-toxic, and biodegradable qualities. Additionally, they can be utilized to administer growth nutrients, medications, and stem cells.

• Hydrogels based on alginate

These hydrogels have the ability to absorb wound fluids and create a barrier that aids in wound healing.

• Hydrogels based on collagen

Higher collagen concentrations in hydrogels can promote tissue regeneration and increase cell viability.

• Hydrogels that conduct

By improving the electrical currents in the skin, these hydrogels can hasten the healing process of wounds

5. Conclusion

Hydrogel-based wound dressings represent a transformative advancement in wound care, offering multifaceted benefits such as maintaining a moist healing environment, regulating inflammation, delivering therapeutic agents, and accelerating tissue regeneration. Their adaptability to diverse wound types, including chronic wounds like diabetic ulcers and venous ulcers, underscores their clinical potential. This review highlights the innovative designs and formulations of hydrogels, including chitosan, alginate, collagen-based, and conductive hydrogels, which exhibit significant efficacy in mitigating inflammation, enhancing cell viability, and promoting rapid wound closure. Despite their demonstrated advantages, certain limitations persist, including mechanical fragility, high production costs, and challenges in eradicating biofilms and infections. Addressing these gaps is crucial to fully realizing the potential of hydrogels as an integral component of modern wound care technologies.

6. Scope of Future

1. Enhancement of Mechanical Properties:

Future research should focus on improving the mechanical strength and elasticity of hydrogels to ensure their stability and durability in challenging wound environments, especially in areas with high mobility.

2. Integration with Advanced Technologies:

- Nanotechnology: Incorporating nanoparticles for enhanced antimicrobial activity, biofilm disruption, and targeted drug delivery.
- 3D Printing: Utilizing 3D printing for patient-specific hydrogel designs tailored to individual wound profiles.
- Biosensors: Embedding biosensors in hydrogels for real-time monitoring of wound healing progress and infection detection.

3. Multifunctionality Development:

Developing multifunctional hydrogels capable of simultaneously addressing inflammation, infection, and tissue regeneration through controlled and sustained release of therapeutic agents, including growth factors, proteins, and stem cells.

4. Personalized Medicine:

Customizing hydrogel formulations to suit the unique characteristics of a patient's wound, such as depth, microbial presence, and chronicity, for optimized healing outcomes.

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