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Review Article

Hydrogel Dressings: Multifunctional Solutions for Chronic Wound Healing; Focusing on *In Vivo* Studies

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ABSTRACT

Approximately, 1 to 2% of the population in developed countries suffer from chronic wounds. Nearly 6.5 million Americans have suffered at least one chronic wound. Chronic wound treatment is critical for patients to maintain their mental and physical well-being and improve their life quality. Chronic wounds can be treated in various ways, including hyperbaric oxygen therapy, debridement, ultrasound, skin grafts, negative pressure wound therapy, electromagnetic therapies, and hydrogel dressings. Hydrogels are among the most viable and promising options since their tunable characteristics, such as adhesiveness, antimicrobial and biodegradability, pre-angiogenic bioactivities, and anti-inflammatory, are beneficial to healing chronic wounds. In *in vivo* studies utilizing animal models, hydrogel dressings emerged as multifunctional solutions for chronic wound healing. These investigations consistently demonstrated that hydrogel dressings accelerated wound healing rates compared to traditional methods and maintained an optimal moist wound environment, which fostered tissue regeneration while minimizing scarring. Moreover, the remarkable biocompatibility of hydrogel dressings became evident in these animal model experiments, as they showed minimal adverse reactions in chronic wound patients. The results of these *in vivo* studies collectively highlight the promising potential of hydrogel dressings as a versatile therapeutic option for effectively managing chronic wounds. This review discusses dressings made of hydrogel in animal models for their multifunctional properties and potential benefits in treating chronic wounds. The efficacy of hydrogel dressings over other kinds of dressings is also demonstrated by providing examples of commercially available hydrogel dressings.

1. Introduction

Skin injuries can be caused by physical or thermal trauma, as well as by medical conditions that can disrupt the body's normal function or result in physiological instability due to these conditions[1]. There is increasing evidence that wound healing is one of the most dynamic biological processes, along with the interaction of biomolecules and stem cells contributing to the repair of wounds at every level[2]. Chronic wound healing can result from any disorder of these factors. Several physiological factors can interfere with the healing process of chronic wounds, such as diabetes, considered the largest cells of the body[3]. The presence of these factors prevents the wound healing process from progressing to the next stage[4]. In addition to the high morbidity, mortality, and recurrence rates associated with diabetes-related chronic wounds, they are one of the leading causes of nontraumatic amputations worldwide[5].

It has been demonstrated in several *in vivo* studies that reactive oxygen species (ROS) promote wound healing by triggering cell migration and angiogenesis[6-8]. Nevertheless,

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large amounts of ROS can impair or halt wound healing, particularly chronic wounds[9]. An inflammatory response to chronic wounds increases ROS production, overriding the cell's antioxidant capacity and preventing wounds from progressing to the proliferative phase[6]. Eventually, it caused chronic wound healing by keeping the wound in an inflammatory cycle for a prolonged period[10]. Therefore, maintaining redox balance in cells to obtain antioxidants may prevent immune system disorders and abnormal cell growth. It has been shown *in vivo* that antioxidation accelerates wound healing, particularly for chronic wounds[11]. Thus, using antioxidants has become an effective method of speeding up the healing process of chronic wounds.

Dressings made from hydrogel are considered ideal candidates for chronic wounds and have already been used *in vivo* [12,13]. With its 3-D structure, improved permeability, great biocompatibility, and ability to provide wound healing in a wet environment, this dressing is ideal for wound healing, it is ideal for wound healing[14]. As a result, traditional dressings no longer have their shortcomings. Antioxidant-infused hydrogel dressings have been developed to speed up chronic wound healing[15]. As a result, chronic wound treatment has become more and more favorable[16]. Chronic wounds can be repaired more rapidly with the antioxidant hydrogel by reducing oxidative stress, improving wound microenvironment, and reducing oxidative stress[17]. With antioxidant hydrogels, chronic wound healing can be accelerated[18]. This review comprehensively describes hydrogels and their role in chronic wound healing. Also, this review discusses dressings made of hydrogel in animal models for their multifunctional properties and potential benefits in treating chronic wounds. The efficacy of hydrogel dressings over other kinds of dressings is also demonstrated by providing examples of commercially available hydrogel dressings.

2. Wound healing

2.1. Acute wound healing

Acute and chronic wounds can be classified based on their nature of wound healing, and follows an orderly and dynamic process[19]. An acute wound, also known as a normal wound, is usually caused by mechanical trauma, burns, or chemical exposure. Usually, it takes 8–12 weeks for the wounds to heal completely, leaving no scars[20]. Healthy skin includes skin layers such as epidermis, subcutaneous, and dermis[21]. 1) The epidermis is the most outer layer of the skin. In addition to effectively controlling water loss, the epidermis also acts as a barrier against external stimulation because of its high impermeability[22]. 2) The dermis is a layer of skin that consists of extracellular fibroblasts, matrix, elastin, and glycosaminoglycan. It provides skin physical support, flexibility, and protection from UV rays[23]. 3) Adipose tissue is well vascularized in the subdermal layer, which regulates skin temperature and gives the skin elasticity. Healing wounds can be better understood by understanding normal skin composition[24].

Recovery from normal tissue injury involves a series of complex processes occurring promptly and orderly[25]. Hemostasis, inflammation, proliferation, and maturation are the four parts of these complex processes[26]. Hemostasis is the first process after injury and bleeding[27]. A wound site's exudates will coagulate with coagulation factors, providing mechanical support for the injured tissue[28]. During the inflammatory stage, debris is removed by monocytes, inflammatory cells, lymphocytes, and macrophages, which prepare wound beds for the formation of granulation tissue[29]. The proliferative process involves the replacement of damaged tissue by fibroblasts and epithelial cells, followed by the formation of granulation cells on the wound's surface[30]. As the final stage, remodeling entails developing connective tissue and new epithelium. These phases are not strictly and explicitly differentiated in terms of period but overlap[31]. Moreover, the duration of the transition overlap period is usually determined by the differentiation and maturation of various wound-healing cells, such as fibroblasts and macrophages.

2.2. Chronic wound healing

According to clinical definitions, a chronic wound is caused by numerous causes that cannot automatically return to normal within three months and show no sign of healing[32]. Further, chronic wounds tend to heal slowly due to potential physiological conditions, such as recurring and diabetes[33]. The most common causes of chronic wounds are sustained stimulation, such as repeated tissue damage, persistent inflammatory responses, or hyperglycemia[34]. Antibiotics is not effective against bacteria if uncontrolled inflammation results in the self-secretion of extracellular polysaccharide matrix[35]. Persistent hyperglycemia can also directly lead to high ROS concentrations in the blood through advanced glycation end products (AGEs)[36]. Consequently, metabolic disorders may affect blood vessel structure and tissue regeneration by disrupting the redox balance of the cells.

There are quite a few hazards associated with chronic wounds. Not only are they challenging to treat promptly, but they also burden patients with substantial financial obligations[37]. Beyond the risk of infection, chronic wounds can also result in amputations and even death[38]. Additionally, these wounds can cause nutritional deficiencies, further weakening the body's resistance and giving rise to various complications. Accordingly, chronic wound healing impairment is more complex and serious than normal healing because it involves much more complex problems and symptoms[39]. A detailed analysis of the causes and hazards of chronic wounds is presented first, followed by a detailed analysis of the specific factors and mechanisms that contribute to chronic wound healing impairments[40].

3. Wound healing treatments

Dressings of the modern age are mostly classified according to the materials they are made of, such as hydrogels, films, and foam boards[41]. Hydrogel dressings prevent fluid loss, purulent substances from accumulating, and crust-forming organisms from infection and propagating bacterial growth [42,43]. They are now regarded as among the best chronic wound treatment materials available[44]. In addition to keeping wounds dry and preventing bacterial infections, traditional dressings also absorb large amounts of exudates, which can lead to infection[45]. Several moisturizing copolymers are designed as hydrogel dressings to absorb large amounts of wound exudate while keeping the wound moist and promoting wound healing[46]. Additionally, wound dressings have been proposed to enhance the migration of leukocytes, promote gas exchange, remove excessive exudates, prevent infection, and even provide heat insulation and prevent reinjury[47]. The development of functional hydrogels led to materials with high biocompatibility and biodegradability and various functions (such as antimicrobial and antioxidative properties, injectable properties, and anti-inflammatory properties)[48]. Due to their multifunctionality and multi-stage combination therapy capability, multifunctional hydrogels are useful in biomedical and pharmaceutical applications[49]. Because antioxidant research is rapidly developing and ROS poses great dangers to chronic wounds, the combination of antioxidant function and hydrogel has attracted much attention, and there have been some new hydrogel dressings developed with antioxidant functions, leading to a revolution in chronic wound treatment[50].

3.1. Wound dressings

To promote wound healing, wound dressings are applied to the wound. For efficient clinical performance, an ideal wound dressing should eliminate or absorbe excessive fluids and exudates from the wound environment while maintaining moisture, prevent bacterial growth, permit gas flow which prevents external trauma to the wound, allow simple removal or biodegradable so that it is not painful to remove and does not damage newly formed tissue, decrease surface necrosis and maintaining cell viability, alleviate wound pain, and affordability[51-53]. Dressings for wounds of different types have been explored. However, their applicability varies according to wound characteristics, for example, the depth of the wound and the amount of fluid exuded. A description of common wound dressing types is provided in the following section.

3.2. Films

In addition to protecting against damage and external contamination, a film dressing keeps the wound environment moist by providing an optically transparent, thin layer of polymeric material[54]. Various properties can be added to them, such as gas permeation, adhesion, and antimicrobial properties[55,56]. Nevertheless, removing a film dressing can be difficult and damage newly formed tissue[57]. Moreover, because the films cannot collect and remove fluid from a wound environment, newly differentiated keratinocytes may be damaged by accumulated fluid[58]. It is important to use dressings that can be easily removed from chronic wounds to reduce the risk of injury to cells and tissues.

3.3. Gauze

In medical terminology, gauze dressings are known as wet-to-dry dressings. An ordinary gauge is a thin, transparent, elastic, gas-permeable, nontoxic, biocompatible, and biodegradable, transparent polymeric material[59]. The weave structure of gauze is free and open. The warp yarns are crossed before and after each pair of weft threads in the weft yarns. It holds the gauze firmly in place. The gauze dressings are used to dry superficial wound debris and adhere to necrotic tissues[60]. Moreover, gauze dressings prevent microbial contamination of wounds. As a result of tissue cooling during the transition from inflammation to the proliferation phase, leukocytes and phagocytes are unable to function properly[61]. Further, gauze can adhere to tissue surfaces, causing hypoxia, vasoconstriction, and re-injury when dried, which may hinder tissue healing[62]. By impregnating gauze with petrolatum, saline, or hydrogels, the functionality is improved[63]. Using these modifications, gauze can maintain wound moisture while preventing local cooling, eliminating adverse effects.

3.4. Foam dressings

The exudates in chronic wounds can be absorbed by foam dressings, which are strong adsorbents[64]. They also insulate the wound area without adhering to it while providing a moist environment. Additionally, foam dressings can be designed with adhesive borders to adhere to the skin without sticking to the wound bed[65]. To keep the dressings secure on the wound, a secondary dressing may be needed[66]. The foam might adhere to the wound unless it is moist or has a high level of exudate.

3.5. Hydrocolloid dressings

Hydrocolloid dressings provide an insulating and moist environment that can protect wounds without infecting them and stimulate the body's natural enzymes so that granulated tissue can be formed[67]. It is also important to note that hydrocolloid dressings have limitations as well. A gel-like fluid drain, with an unpleasant odor, might result from their over-promotion of granulation tissue. A hydrocolloid dressing may also have difficulty treating wounds around cavities[68]. This method indeed has several advantages when it comes to wound healing. Still, other new and more convenient methods make the treatment of chronic wounds more efficient and comfortable[69] (Figure 1).

4. Healing chronic wounds with functional hydrogels

The properties of hydrogels can be multifunctional.

Figure 1. Different types of wound dressings commonly used in clinical practice. Each dressing type is briefly described, including films, gauze, foam dressings, wound fillers, hydrocolloid dressings, and hydrogel dressings. The figure visually showcases the unique characteristics and applications of each dressing type, helping healthcare professionals make informed choices for wound management. The choice of wound dressing depends on factors such as wound depth, exudate levels, and desired wound healing outcomes, making this figure a valuable reference for medical practitioners and researchers in the field of wound care.

Hydrogels for chronic wound healing can incorporate a variety of functional characteristics, such as biocompatibility, biodegradability, adhesiveness, vascularization potential, antimicrobial, anti-inflammatory, and proangiogenic properties[70]. To maintain tissue homeostasis during chronic wound healing, a hydrogel must be biocompatible to present a matrix suitable for local tissues without causing damage. As with fibroblast proliferation, re-epithelialization and neovascularization, and chronic wound remodeling, hydrogels' biodegradation and biodegradability rate are essential factors[71]. As well as keeping the wound moist, enhancing the homeostatic effect, and absorbing exudates during healing, hydrogel dressings are also highly stable when they have high bioadhesive[72]. It can be beneficial to prevent infections using antimicrobial hydrogels since prolonged healing of chronic wounds increases the risk of infection. Chronic wounds are delayed in healing mainly due to the inflammatory phase, as described before. In a recent *in vivo* study, an anti-inflammatory hydrogel can shorten the healing period by easing the transition from inflammation to proliferation[73]. Delays in chronic wound healing may also be due to inadequate oxygen and nutrient delivery[74]. It is possible to accelerate chronic wound healing by applying proangiogenic hydrogels that stimulate angiogenesis. Drugs or therapeutic agents can be incorporated into hydrogels to enhance their functionality. The release of drugs or therapeutic agents is controlled and sustained by hydrogels. Chronic wounds can be treated with hydrogel-based wound dressings in various ways[75].

4.1. Chronic wound healing with biodegradable hydrogels

A biodegradable material decomposes when it comes into contact with a biological environment[76]. As a result, the biodegradation rate of hydrogels is of special significance in the healing and regeneration of chronic wounds, especially those caused by burns and diabetes-related foot ulcers, which can be particularly challenging to treat[77]. There should be a matching rate between the degradation rate and new tissue formation and remodeling rate. Different strategies may be employed to tailor biodegradability rates, such as changing polymer chain crosslinking degrees, blending/combining different polymers, or introducing protease-sensitive chemical functional groups[78]. Collagen and gelatin are commonly used as ECM-derived polymers to make biodegradable hydrogels[79]. Controlled enzymatic biodegradation and cell attachment during the remodeling and proliferation of tissues are made possible by these biomaterials' intrinsic cell recognition molecules[80]. Physical crosslinking of collagen and gelatin leads to the formation of hydrogels when the temperature changes. Physiological temperatures, however, do not allow gelatin to retain the intact hydrogel structure[81]. The stabilization of gelatin-based hydrogels is commonly achieved through cytocompatible chemical crosslinking. Photocrosslinkable hydrogels are often formed by modifying gelatin with methacrylates (GelMA)[82]. Rapid degradation can be an issue when gelatin-based hydrogels are applied to wounds, but increasing gelatin concentration and polymer chain crosslinking can help tailor degradation behavior[83]. Biodegradable natural hydrogels based on polysaccharides, such as chitosan, dextran, and alginate, are also widely used in chronic wound healing in a recent *in vivo* studies[84]. They can enhance wound healing by enhancing granulation, neoangiogenesis, and migration, but they degrade more slowly than ECM-derived protein-based polymers[85,86]. In wound healing, hydrogels made from proteins and polysaccharides were shown to degrade acceptably when mixed, blended, or chemically crosslinked[87]. Based on the amount of gelatin in the mixture and the extent of photocrosslinking, the degradation of chitosan was reduced when methacrylated chitosan (ChMA) was mixed with gelatin[88-90]. Hyaluronic acid (HAMA) and GelMA were photocrosslinked in another study to form a hybrid hydrogel[91]. Compared to pristine GelMA hydrogels, GelMA hydrogels with stronger covalent bonds have a greater resistance to collagenase biodegradation[92].

4.2. Chronic wound healing with bioadhesive hydrogels

It can provide long-term stability by using bioadhesive hydrogels to adhere hydrogel dressings to wet wound beds[93]. Hydrogels are flexible and stretchable, providing comfort to patients with wounds. Bioadhesive hydrogels can be removed more easily from wounds than conventional wound dressings, such as films and gauze[94]. It is possible to impart the bioadhesive properties of hydrogel dressings by modifying them with polyphenol-derived moieties, such as catechol, dopamine, gallic acid, or tannic acid[95]. Modifying polyphenol-derived moieties can tailor adhesive properties to meet particular wound needs. Those with shallow or small chronic wounds benefit from highly adhesive hydrogel dressings, while those with deep or large chronic wounds benefit from less adhesive dressings[96]. CS-GA has strong biocompatibility, adhesive properties, and stretch capabilities. With greater amounts of GA grafted, the bioadhesion capacity was enhanced[97]. The GA modification also enhanced antioxidant and antibacterial properties, depending on the concentration of ROS scavenging[98]. CS-GA hydrogels healed skin defects more efficiently than gauze and gelatin sponges in an *in vivo* model[99]. They found that wound closure was better with CS-GA dressings due to their enhanced bioadhesivity and antioxidant activity.

4.3. Chronic wound healing with antimicrobial hydrogels

Hydrogel dressings provide an initial barrier to microorganism invasion into the wound bed. In chronic wounds, however, infection risks rise due to prolonged healing and excessive inflammation[100]. Various *in vivo* studies stated the antimicrobial activity of hydrogels with antibacterial, antiviral, and antifungal components[101,102]. Inorganic materials or antibacterial agents are commonly incorporated into hydrogels to create antibacterial hydrogels[103,104]. The most often used antibacterial agents for treating chronic wounds are organic compounds such as vancomycin, gentamicin, ciprofloxacin, fluoroquinolones, hematoporphyrin, penicillin, moxifloxacin, and cephalon-sporins[89]. These antibacterial agents prevent bacterial growth by blocking DNA duplication or protein synthesis. To prevent drug resistance, antibacterial agents must be released from the hydrogel again and again[105]. By controlling the hydrogel's stiffness, swelling, or degradation properties, antibacterial agents can be released more effectively[106]. Gold (Au) and silver (Ag) ions or their nanoparticles (NPs) have been used in *in vivo* studies for thousands of years to enhance wound dressings with antimicrobial properties[107]. After stabilizing them into microvesicles, such as liposomes, they can be loaded into hydrogels directly, or they can be loaded directly into hydrogels before stabilizing them. It is very easy to control the morphology, particle size, and surface chemistry of the hydrogel particles to control the antimicrobial performance of hydrogel wound dressings[108]. A recent *in vivo* study found that Ag^+ and Ag NPs exhibit the highest antimicrobial activity in mammalian cells at appropriate amounts because they are both cytotoxic to mesophilic cells[109]. When Ag NPs are incorporated into hydrogels, they are effective against Gram-positive and Gram-negative bacteria.

It has also been demonstrated in an *in vivo* study that metal oxides can be incorporated into hydrogels to promote chronic wound healing[110]. Several materials have been reported to have antibacterial properties, such as zinc oxide (ZnO), titanium dioxide (TiO2), and copper oxide (CuO2) *in vivo*[111]. Only certain types of bacteria resist some metal nanoparticles' antibacterial properties. Antibacterial properties are inherent to some hydrogels. Among its properties is inherent antibacterial activity, such as Chitosan[112]. In addition to modifying membrane permeability, its polycationic structures interact electrostatically with the positively charged bacterial cell wall.

4.4. Chronic wound healing with anti-inflammatory hydrogels

Hydrogels that reduce ROS levels and enhance macrophage recruitment to wound beds are anti-inflammatory[113]. Through these functions, wound healing is facilitated by inflammation, allowing for proliferation to take place, allowing the process to move forward, reducing healing times, and increasing healing speeds[114]. It has been shown that some hydrogels have intrinsic anti-inflammatory properties[115]. Inflammatory responses can be regulated by CS and its derivatives, which help enhance the secretion of TGF-β, IL-1, and PDGF, accelerating angiogenesis, collagen production, and proliferation[116]. The ECM of the skin contains significant amounts of HA, which has inherent anti-inflammatory properties. A signaling cascade involving HA is believed to contribute to HA's

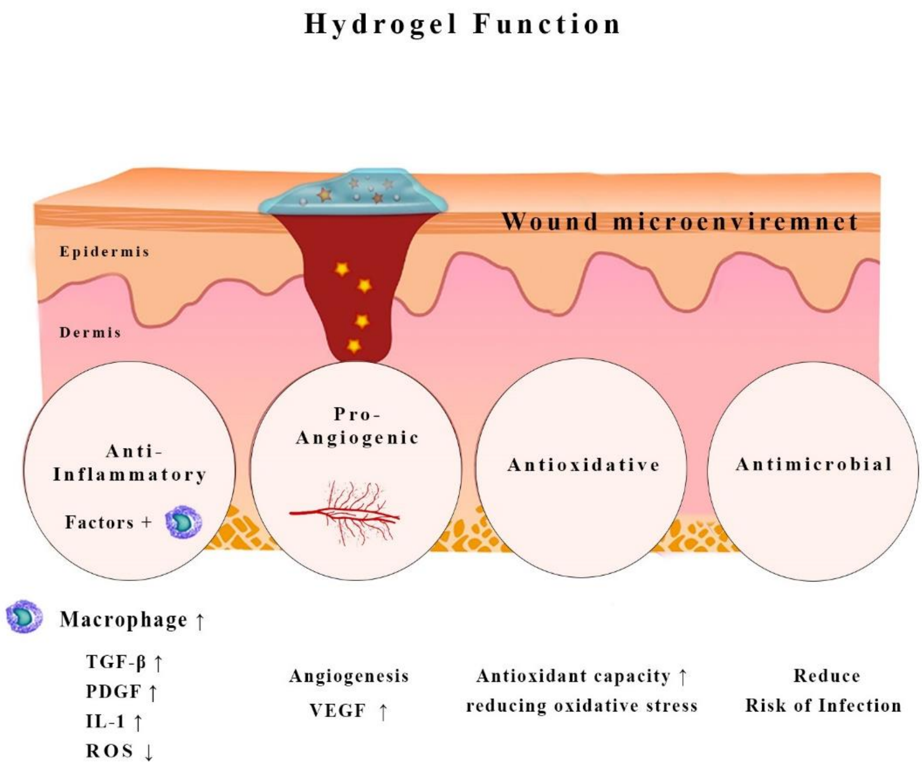

Figure 2. Key factors influenced by hydrogel wound dressings in the wound healing process. Hydrogels can enhance wound healing by increasing the recruitment of macrophages, promoting angiogenesis, reducing levels of reactive oxygen species (ROS), and decreasing the risk of infection. Pro-angiogenic hydrogels stimulate the formation of new blood vessels, while antioxidative hydrogels lower ROS levels. Additionally, antimicrobial hydrogels reduce the risk of infection by incorporating antibacterial, antiviral, or antifungal components. These attributes make hydrogel wound dressings valuable in facilitating effective wound healing by positively impacting critical factors within the wound microenvironment.

function in recruiting inflammation cells around wounds, releasing cytokines, and reducing inflammation through this involvement[117]. A chemically attached anti-inflammatory agent, such as phenolic substances, can also add anti-inflammatory properties to hydrogels[118,119]. In addition to plant extracts, antimicrobial peptides, and honey, these compounds can be obtained in other ways. The immune modulatory pathways recognize anti-inflammatory compounds to reduce inflammation and ROS levels around wounds[120]. To improve anti-inflammatory properties, targeting agents can be added to hydrogels to stimulate the body's innate immune system[121]. It has been suggested that a sphingosine-1-phosphate receptor target may facilitate the activation of inflammatory cells, which has been shown to aid in wound healing by transitioning from an inflammatory state to a proliferative state[122]. Wound healing applications can also benefit from hydrogels containing bioceramics. A bioceramic particle encapsulated in gelatin/PCL nanofibers was shown to release silicon (Si) ions under controlled conditions, thereby reducing inflammation, increasing angiogenesis, and reinforcing epithelium[123].

4.5. Healing chronic wounds with drugs

To facilitate wound healing, hydrogels can be combined with various types of drugs and therapeutic agents to increase the healing process[124]. It is of prime importance that the proteins are released from the hydrogel in a controlled and sustained manner so that their properties can be maximized[125]. A smaller pore size and a stiffer shape can lead to a more gradual release of physically encapsulated drugs than hydrogels with larger pores and softer shapes[126,127]. There is a direct correlation between the size of the pores in a hydrogel and the speed at which drugs are released from it. This can decrease the efficacy of medications. The covalent bonding of drugs to hydrogels enables controlled release kinetics of drugs even at low drug concentrations[128,129]. Delivering controlled amounts of drugs is possible using stimuli-responsive hybrid hydrogels[130]. PH, glucose levels, and temperature in the wound environment can alter these hydrogels' physicochemical and biological properties[131]. Diabetic foot ulcers, for instance, are characterized by an acidic environment due to high glucose levels[132]. An acylhydrazone and imine bond between N-carboxyethyl CS (N-CS), adipic acid dihydrazide (ADH), and HA-aldehyde (HA-ALD) was utilized to develop a hybrid hydrogel (Gel)[70]. Insulin was incorporated into the Gel to release insulin when the wound's acidity rises (In+Gel). Labile acylhydrazone bonds were found to release insulin in response to an acidic pH. In a recent *in vivo* study, collagen deposition, glucose levels decreased in a rat model, and a full-thickness wound healed effectively (Figure 2).

5. Conclusion

Hydrogel dressings are versatile and multifunctional tools for chronic wound healing. They maintain a moist wound environment, promoting tissue regeneration and reducing the risk of infection. *In vivo* studies have provided concrete evidence of their efficacy in accelerating wound healing, reducing inflammation, and stimulating tissue repair. These studies also underscore their ability to enhance angiogenesis and oxygenation, which are crucial for the wound healing process. Hydrogel dressings' adaptability to various wound types makes them valuable in real-world clinical settings. Their continued use in *in vivo* research highlights their clinical relevance, and ongoing advancements in this field are expected to further improve their effectiveness in managing chronic wounds. Patients and healthcare professionals can anticipate enhanced quality of life and faster healing times as these innovative dressings continue to evolve and meet the complex challenges of chronic wound care.

Declarations

Competing interests

The authors declare no conflict of interest.

Authors' contributions

Alireza Azizi led the conceptualization phase, framing the study's core ideas and objectives. The writing of the initial draft was skillfully undertaken by Ahmad Mir Hosseini, Mohammad Amin Salim, and Parisa Pourfaraziani, who dedicated themselves to the creation of the manuscript. Mohadeseh Jamali, Negar Agahi, and Mahsa Mohammadian played a critical role in meticulously reviewing and editing the content, ensuring its quality and precision. The project was made possible through self-funding, ensuring the research's independence and autonomy. Throughout the project, Alireza Azizi provided essential supervision and guidance. All authors checked and approved the final version of the manuscript for publication in the present journal.

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Ethical considerations

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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