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New Treatments for Management of Diabetic Foot Ulcers

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Abstract

Diabetic foot ulcers (DFUs) are one of the more common problems linked with diabetes. DFUs are persistent wounds which frequently result in non-traumatic lower limb amputations owing to ongoing infection and other ulcer-related complications. Furthermore, these difficulties place a major fiscal strain on the healthcare system since costly medical procedures are necessary. Furthermore, the therapeutic therapies that are now accessible have only been fairly successful, indicating a significant need to discover innovative ways for the better treatment of DFUs. Hydrogels are 3-D structures made from natural and/or synthetic polymers. Because of their unusual adaptability, tunability, and hydrophilic qualities, these materials have received substantial research for a variety of medicinal applications, including drug delivery and tissue manipulation. As a result, this review article examines the most recent improvements in hydrogel wound dressings for successful DFU therapy, offering an overview of current viewpoints and problems throughout this study area.

Keywords: Hydrogel, Diabetic foot ulcers, Wound dressing, Diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a long-term global pandemic illness. Based on statistics released by the American Diabetes Association (ADA) and epidemiological studies, the worldwide financial impact of diabetes will exceed $2.1 trillion by 2030, corresponding to 2.2% of global GDP (1). Diabetes may lead to serious impairment such as blindness, diabetic retinopathy, kidney failure in its final stages, and lower limb amputations. The psychological and physical consequences on sufferers are severe and hard to treat (2). Diabetic foot ulcers (DFUs) are a serious DM-related disease that is usually associated with greater mortality and premature mortality. It impacts about forty to sixty million diabetes individuals globally and is distinguished by the development of persistent sores caused by a combination of metabolic abnormalities, nerve injury, insufficient blood supply, and biomechanical alterations in the lower limbs (3). DFUs may ultimately result in persistent damage, infection, and, in the most severe case, lower limb amputation, which is predicted to happen every thirty seconds worldwide (4). At present, treatment options for DFU include debridement, pressure release ("off-loading"), antimicrobial agents, and revascularisation. Nevertheless, in many situations, conventional treatments fail to provide complete wound healing, emphasizing the need for creative options that stimulate tissue repair while avoiding wound-related problems (5).

In this regard, wound dressing technology has received increasing interest as a possible path for developing clinically successful DFU therapy. The optimum dressing for treating persistent wounds,

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including DFUs, must meet many fundamental necessities: (1) provide moisture that promotes tissue healing; (2) inhibit bacterial infiltration within the lesion; (3) have suitable porosity for gas exchange; (4) encourage cell movement, growth, and new blood vessels formation; and (5) be sterile, biocompatible, and easily replaced (or biodegradable). Hydrogels, which are polymeric three-dimensional (3D) substances, have shown promise for effective DFU dressing manufacturing. First, hydrogels are very biocompatible (6, 7). This enables them to imitate the normal ECM microenvironment and offer an optimal setting for cell growth. Second, hydrogels are very water-retentive and permeable. Because of the existence of crosslinked networks, hydrogels may have a water content of as high as 96%, allowing for environmental hydrating and keeping the wound wet (8). Furthermore, the presence of a hollow network architecture creates an optimal environment for gas exchange and nutrition transfer. Third, because of their distinctive structural features, hydrogels do not produce further mechanical harm. As a result, the primary goal of this study was to analyze recent breakthroughs in the production of hydrogel-based wound-dressing platforms, with an emphasis on manufacturing techniques and effectiveness in relation to DFU therapy (6, 8).

Wound healing processes in normal condition

Wound healing is a normal physiological response to tissue damage. Wound rehabilitation, on the other hand, is a complicated procedure involving different kinds of cells, cytokines, mediators, and the vascular system (9). The process of early vasoconstriction of blood arteries and accumulation of platelets is intended to halt bleeding. This happens followed by the entry of various inflammatory cell types, beginning with neutrophils. These inflammatory cells, in turn, produce several cytokines and mediators which encourage blood vessel development, thrombosis, and reepithelialization (10). Fibroblasts, in turn, lay down extracellular elements that will function as scaffolds. The inflammatory stage is marked by hemostasis, chemotaxis, and enhanced permeability of the vessels, which prevent further harm, close the wound, remove cellular debris and microorganisms, and promote cellular movement. The inflammatory stage normally lasts a few days. Granulation tissue, reepithelialization, and neovascularization are all hallmarks of the proliferative stage. This period might extend for many weeks. In the third stage, the wound reaches its maximum strength during the stages of maturation and regeneration (11, 12).

A summary of wound regeneration at DFUs

The immune cells, both innate and adaptive, that make up the skin's immune microenvironment are found throughout each layer of the epidermis and dermis. They communicate with tissue cells like fibroblasts, keratinocytes, and vascular endothelial cells to support tissue repair and immunological equilibrium (13). Emerging data points to the critical functions of immune system cells and the immunological milieu in the healing procedure and restoration. Immunomodulation is involved in all four conventional wound healing phases: hemostasis, inflammation, proliferation, and remodeling (14). DFUs are often associated with immunological disorders, as shown by the failure of macrophage phenotypic transitions under pathogenic circumstances. DFUs are linked with chronic and severe inflammation, an aberrant immunological environment, numerous infections, poor blood vessel development, and delayed re-epithelialization (15). DFUs are unable to reach their proliferative phase owing to several biological reasons. Improving the shift of diabetic wounds from the inflammatory to the proliferative phase is a possible method for expediting wound recovery (16). In addition, MMPs impede the activity of growth factors, reducing angiogenesis and tissue oxygenation, leaving a wound hypoxic and persistently open. As a result, exposed lesions are more susceptible to pathogenic diseases, which increase due to the reduced phagocytosis activity caused by hyperglycemia (17). The interaction of all of these variables leads to even more serious health consequences for the patient. To address this problem, tissue engineering methods have permitted the construction of hydrogel-based platforms which act as frameworks that facilitate appropriate cell communication and occupy the injured area with bioactive substances which encourage re-epithelialization, reduce inflammation, accelerate rehabilitation, and enhance the development of scars (18).

Management of DFUs with hydrogel-based wound dressings

Although various kinds of dressings, such as hydrocolloids, foams, and alginates, are currently accessible for DFU administration, novel dressings that satisfy the stringent demands for proper wound debridement, appropriate systemic therapy with antibiotics, and regular replacement of dressings and wound examination are highly sought after (19). Hydrogels are very interesting options for the management of DFU because of their distinctive characteristics that promote wound regeneration. Multiple factors influence how hydrogels handle DFU. To begin, hydrogels' a great deal of water aids in the maintenance of a moist wound circumstances, which is required for effective wound recovery (20). The abundance of water in the hydrogel allows the

interchange of nutrients as well as oxygen among the wound bed and the tissues that surround it, resulting in a condition critical for cellular metabolism, tissue reconstruction, and the recovery process. Second, hydrogels are capable of absorbing and holding wound fluid, which helps to prevent inflammation and bacterial development (19). The absorption of fluid prevents the wound from developing a crust or scab, which may hinder recovery and raise the chance of infection. One of the primary benefits of hydrogels for DFU therapy is their capacity to discharge bioactive molecules including growth factors, which promote wound reconstruction, and cytokines and antimicrobial substances, which enable the movement of cells and avoid infection (21). Hydrogels, in especially, may be used as medication delivery vehicles, permitting the regulated and long-term discharge of bioactive substances at the site of injury. A new study found that a hyaluronic acid-based hydrogel filled with basic fibroblast growth factor (bFGF) hastened wound healing and improved revascularization in a DFU rat model. Furthermore, certain hydrogels contain inherent antibacterial properties that may help eliminate infections and enhance wound rehabilitation. In recent years, a chitosan-based hydrogel demonstrated remarkable antibacterial action on *Staphylococcus aureus* and *Escherichia coli* and hastened wound regeneration in a diabetic rat model (22, 23).

Natural hydrogels for diabetic wound management

Collagen based hydrogels

DM is a serious issue with DFU and the most prevalent DM consequence. A number of creative methods has been extensively created to address this crucial problem, including collagen, which is believed to be the most (24). Collagen (Col) polymer has been identified as the most attractive choice due to its capacity to swell in water, mechanical qualities, and gelling capability. Col may be obtained from a variety of sources, however animal collagen is now the most common source of col products, with the majority of them made from raw materials including cow products. Most col compounds are manufactured from bovine and porcine skin and many components (25). A hydrogel is made of water, which promotes diffusion of medication and preserves hemostasis. Collagen type I (Col-I) is believed to be necessary for attracting growth factors to the damaged area and initiating wound recovery and tissue repair. Nevertheless, in the chronic foot ulcer scenario, the epidermis is ruptured, causing the breakdown of the extracellular matrix and cellular structure damage, which results in Col-I insufficiency (26). Furthermore, it inhibits the normal growth and expansion of fibroblasts to the wound region, thereby slowing down the recovery process. Col is a biocompatible structural protein, with less immunogenicity, biodegradable, and biomimetic, which makes it an ideal source of biological materials for tissue engineering and regenerative medicine (24). The composition and functionality of the collagen fibres influence the cellular response that is commonly regulated by integrin. This phenomenon is achieved by a biological process that is known as fibrillogenesis. Fibrillogenesis is a process of col network formation and interaction within the cellular level to form a higher-order three-dimensional structure. Furthermore, its function in MMP inactivation assists in retaining favorable metabolic equilibrium and humidity levels in the damaged area (27, 28).

For example, Lei et al. investigated the efficacy of collagen hydrogels to stimulate revascularization and wound repair in diabetic rodent models. To do this, deep injuries were created and treated externally using a collagen hydrogel containing recombinant human epidermal growth factors. Following fourteen days of therapy, rats administered with the created hydrogel had considerably lower wound regions, suggesting quicker damage repair, when compared to the group that wasn't given hydrogel therapy (29). In terms of blood vessel development, the suggested hydrogel treatment promoted both endogenous collagen production and the creation of vascularized scar tissue. In addition, Munish and colleagues conducted a comparative case-control research and found that using a collagen-based covering greatly improved wound recovery (30). The treatment's efficacy was assessed in a trial of twenty-five individuals who had persistent DFU. The wound location was effectively assessed weekly during the initial week of therapy to the 12th week. During the first week of examination, two participants were entirely repaired, while 12 exhibited a considerable decrease in lesion diameter. In addition, the 12-week examination revealed that 21 patients recovered and four had ulcer decrease. Since collagen biological substances are slowly decomposed, it may operate as a temporary bio-template for cell adhesion, migration, and development, as well as fast wound development (31).

Chitosan-based hydrogels

Chitosan (Ch) is a flexible hydrophilic and cationic natural polymer that is neither poisonous, carcinogenic, or immune-stimulating. It consists of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine molecules. It is referred to as water-soluble chitin and is derived from chitin by alkaline deacetylation (32). Chitin is composed of unbranched chains of β-(1-4)-2-acetamido-2-acetamido-2-deoxy-D-glucose. Chitin occurs naturally in mushrooms, green algae, and various microbes, including yeast and fungus. In addition, it originates from

invertebrates including crab shells and insect cuticles (33). Ch's solubility, appearance, and rheological characteristics are all determined by its molecular mass and quantity of acetylation. Crossover, graft co-polymerization, carboxymethylation, etherification, and esterification should be emphasized as the key ways for functionalizing the Ch framework among particular chemical procedures in order to boost their possibilities (34). In general, Ch has shown promise in pharmaceutical fields, notably as carriers of drugs with specific wound treatment uses, such as DFUs. In this regard, Ch has just been demonstrated to be a desirable component for the production of hydrogels using additive manufacturing methods for creating porous three-dimensional scaffolds with precise forms and biological action for the effective regeneration of complicated structures (35).

Xue and colleagues developed Ch-Matrigel-polyacrylamide hydrogels to aid in the recovery of injuries and reconstruction of the skin. These hydrogels have excellent porosity shape, with pore diameters ranging from 20-30 μm, that can keep humidity. This is beneficial for cell movement, adherence, and survival. These hydrogels demonstrated excellent mechanical characteristics, including high fracture strain, compression, tensile strength, and durability (36). Masood et al. developed a Ch-polyethylene glycol (PEG) hydrogel containing silver nanoparticles for diabetic wound treatment. The average size of particles was 99.1 ± 2.3 nm. The hydrogel had an acceptable porosity of 72.2%, which helped to rapid wound repair by suggesting adequate oxygen transmission and exudate absorption. Plain hydrogels have much higher swelling capabilities than nanoparticle-loaded hydrogels. In vitro investigations showed that the polyvinyl alcohol/chitosan/FEN (PCF) hydrogel is highly biocompatible and has considerable antibacterial, pro-angiogenic, ROS-scavenging, and anti-inflammatory capabilities (37). Further animal investigations revealed that the PCF hydrogel may enhance blood vessel development and the accumulation of collagen. The PCF hydrogel significantly reduced the amount of TNF-α and IL-6, indicating its anti-inflammatory action. These striking results highlight the PCF hydrogel's prospective applicability in the management of ulcers caused by diabetes (38).

Artificial and semi-synthetic hydrogel for management of DFUs

Bio-functionality and physical characteristics are also important factors in developing a viable hydrogel covering for DFU therapy. While natural hydrogels have excellent bio-features, their mechanical qualities and manufacturing dependability must be enhanced. Artificial polymers, on the other hand, are more versatile owing to their distinctive features, which may be precisely altered using specialized physical/chemical alteration techniques (39). More crucially, artificial polymers be manufactured on a large scale. Synthetic polymer-based hydrogels often have more uniform and homogenous architectures than natural polymer-based hydrogels, as well as higher water absorption effectiveness due to their highly patterned hydrophilic and hydrophobic domains (39).

Polyethylene Glycol (PEG)

PEG-based hydrogels are currently used to create biological structures owing to their high biocompatibility and tolerance to protein attachment. The incorporation of functional compounds leads to PEG derivatives including polyethylene glycol diacrylate (PEGDA) and polyethylene glycol dimethacrylate (PEGDM), which may also be chemically crosslinked to generate durable matrices which permit tethering or embedding of biomolecules and encourage appropriate healing of tissues (40). Discovering creative techniques to decrease toxicity and improve the biological capacity of PEG-based treatments is so critical. One viable technique is to cross-link PEG with Ch to generate hydrogels that can be loaded with silver nanoparticles (Ag-NPs), which have excellent antibacterial, antioxidant, anti-inflammatory, and anti-platelet capabilities (41). These enriched Ch-PEG hydrogels exhibited significant porosity and swelling, as well as enhanced antioxidant and antibacterial properties against *P. aeruginosa*, *E. coli*, and *S. aureus*. Furthermore, infused hydrogels helped diabetic rabbits repair their wounds faster. Wu et al. also mixed four-armed aldehyde-terminated PEG (4-arm PEG-CHO) with quaternized Ch to generate a hydrogel for the loading of deferoxamine (42).

Polylactic Acid (PLA)

PLA is an aliphatic polyester that may be readily produced in an environmentally friendly manner by condensing lactic acid and then polymerizing cyclic lactides. PLA's biocompatibility, biodegradability, and generally excellent mechanical qualities make it a promising material for medical use (43). Furthermore, it has been linked to increased cell proliferation and growth factor signaling owing to its intrinsic properties that resemble natural collagen fibers in the extracellular matrix. PLA's limited hydrophilicity limits its therapeutic usage, which may be overcome by mixing it with other substances or loading it with biological substances (44). Yu et al., for example, created porous PLA nanofiber membranes and then coated them with sulfated chitosan (SCS) and polydopamine-gentamicin (PDA-GS). The combination of SCS was utilized to increase the hydrophilic properties of PLA tiny fibers and promote M2 macrophage polarization,

whereas PDA and GS were employed to enhance anti-inflammatory and antimicrobial properties (45). In addition, Di Cristo et al. created co-electrospun fibers from PLA and PVP that contained quercetin (QUE), an active compound with potent anti-inflammatory, antioxidant, antibacterial, and wound rehabilitation effects. The produced fibers showed strong hydrophilic properties and a rapid onset of QUE, which was followed by a steady and consistent release for up to 120 hours (46). Furthermore, these nanofibers demonstrated significant antibiofilm activity against S. aureus and anti-inflammatory potential in PMA-differentiated THP-1 macrophages, making them promising options for the successful therapy of diabetic foot infections (46).

Zwitterionic gels

Other artificial substances receiving attention in the area of diabetic wound recovery are hydrogels made from zwitterionic monomers, which have the same negative and positive charges on the same molecule (47). Because of its tightly repeated and strong charge framework, zwitterionic substances have been demonstrated to be excellent in resisting non-specific protein adsorption. As a result, this conduct may help to reduce the inflammation that occurs in injuries by reducing foreign body responses (48). For instance, a single investigation identified through H&E staining that a zwitterionic hydrogel (poly(carboxy betaine methacrylate) (PCBMA)) inserted in mice possessed substantially fewer inflammatory cells than a non-zwitterionic hydrogel (poly(2-hydroxyethyl methacrylate) (PHEMA)), suggesting that a weaker inflammatory reaction could be caused by the capacity of zwitterionic to resist protein adsorption (49). Furthermore, zwitterionic hydrogels may be manufactured with a broad variety of viscoelastic properties and pharmaceutical release capabilities, demonstrating their applicability for external wound healing uses (50).

Additional polymer dressings

Films

Films are smooth, elastic constructions made of clear polymers. Films are frequently employed in wound restoration due to the following benefits: the film surface has tiny holes which enable the transfer of gases blocking bacterial attack; their translucency allows modifications to the wound to be noticed without no removing the clothing; and they are soft and well-fitted to the skin (51). Furthermore, film has an autonomous debridement function, that permits it to dissolve layers and necrotic tissues while treating DUs. Absorption is an important feature of wound dressings. Because the majority of films lack hydrophilic molecules or extremely tiny holes, they offer inadequate water absorption and are hence only suitable for use on moderately oozing lesions (52). Nevertheless, diabetic wounds involve significant harm and exudate. To better address the demands of DU therapy, scientists created nanofiber films that can be readily manipulated and have adjustable pore diameters (46).

Sponges

Sponges are materials having interconnecting porous structures that have been freeze-dried. As previously stated, the size and variety of holes are directly proportional to the capacity to absorb discharge, and sponges' interconnected pores offer the structural foundation for their high water absorption. Furthermore, the great porosity of sponges allows for appropriate oxygen supply, nutrition delivery, and cell growth at the wound site (53). Furthermore, sponges are lightweight and feel gentle on the skin. Because of these benefits, sponges are commonly employed in the treatment of moderate to heavy oozing injuries, such as DUs. Ch is the most often utilized carbohydrate in sponge manufacture (54). Within the several forms of polymers, the distinct cationic linear arrangement of CS, is a deacetylated version of chitin. As previously stated, chitosan's antimicrobial capacity and low immunogenicity meet the fundamental needs of a dressing, whereas its additional biological properties, including biocompatibility, ability to degrade, antioxidant properties, and in situ gelation, which lays the groundwork for its multiple uses when used in a dressing. Nevertheless, sponges' drawbacks, such as weak adhesion, limited mechanical strength, and inadequate antibacterial characteristics, restrict their practical use (55).

Foam dressings

They typically comprise hydrophilic polyurethane foam and are intended to absorb wound fluid while maintaining a wet wound area. Foam dressings may incorporate extra absorbent substances like viscose and acrylate fibers, superabsorbent polyacrylate particles, or silicone coating for non-traumatic disposal (56).

Challenges and conclusions

Hydrogel dressings have shown potential in the management of DFU owing to its capacity to maintain a wet wound environment, stimulate wound regeneration, and alleviate pain. Nevertheless, using hydrogel dressings for DFU therapy has various problems. Diversity in the structure and features of hydrogel dressings is one of the most significant issues (57). Hydrogel dressings may be created from a wide range of polymers, that have unique features like water absorption, biodegradability, and mechanical strength. The kind of polymer used may have a major

influence on the dressing's ability to promote wound recovery. In addition, the characteristics of hydrogel dressings might differ based on the production procedure, resulting in variable effectiveness. A further issue is the requirement for regular dressing changes (40). Hydrogel treatments are intended to provide wet injury circumstances, however, too much moisture may cause ulceration of the skin around them and slow healing. To avoid the wound bed from being overhydrated, hydrogel dressings must be replaced regularly. Individuals may find repeated removal of dressings irritating and raise their risk of infection (58).

Finally, hydrogels have shown considerable promise as a treatment for DFU. They offer a humid environment that aids in healing wounds and may be programmed to release a variety of bioactive substances that encourage the growth of new tissues. In addition, the hydrogels may adapt to the wound bed, creating an additional defense against further damage and bacterial infections. In the meantime, it is important to remember that specific patient features, like wound dimensions and seriousness, must be considered while selecting suitable wound dressings. Yet, much remains to be discovered about the unique features of hydrogels which make them good wound care products, but current study suggests that they are a potential alternative for DFU therapy. With future advances in material science and ongoing research, hydrogels have a chance to greatly enhance the standard of life for patients suffering from DFU.

Authors's Contribution

Shadi Zekri was involved in the conceptualization, design and writing of the manuscript draft. The author read and confirmed the final manuscript.

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