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New biological dressings in diabetic wound healing: Dual effects of anti-infection and immune regulation

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Abstract. As a global epidemic, one of the complications of diabetes is chronic difficult heal wounds, especially infectious wounds, which pose a major threat to the quality of life and prognosis of patients. Traditional dressing materials (gauze, film, foam) often have limited effect, and can easily lead to prolonged treatment cycles and antibiotic resistance. In recent years, as an innovative wound management strategy, biological dressings (hydrogels, fiber scaffolds, microneedle patches) have attracted extensive attention due to their antibacterial effect, inhibition of infection, regulation of the body's immune system, promotion of tissue repair, and good biocompatibility. Here, we discuss the impact of diabetes on the body's immune system, tissue cells, and metabolic processes. In addition, we reviewed the specific mechanisms of different biological dressings in the treatment of diabeti-infected wounds. Finally, we discuss current challenges and future research directions.

Keywords: Diabetes, Infected wound, Immune system, Biological dressing

1. Introduction

As a global chronic metabolic disease, diabetes affects 463 million people worldwide. It is estimated that the number of patients with diabetes will increase by 25% by 2030 [1]. One of the complications of diabetes is diabetic wounds. The healing process of such wounds is unusually slow and often complicated by microbial infection and long-term inflammatory response [2]. According to statistics, about 42.2% of diabetic patients will be affected by diabetic wound infection. If not treated properly, these wounds may lead to limb amputation or even death [3, 4]. It can be seen that the high incidence and mortality of diabetic wound infection, as well as the high medical costs, are major public health problems facing the world [2]. Due to the long-standing hyperglycemic environment, diabetic patients have undergone a series of subtle and profound changes in their immune system, tissue cells, and metabolic processes. These changes work together to greatly hinder the normal healing path of infected wounds, increasing the difficulty and complexity of treatment [5-9]. Although there are many traditional treatment methods, such as negative pressure drainage, skin transplantation, and surgery, these methods still have limitations [10]. As for the traditional dressing materials such as gauze, film, and foam, although they provide physical protection to prevent further mechanical damage to the wound to a certain extent, these traditional materials often lack pertinence, coupled with impaired immune system function of diabetic patients, this physical protection is not enough to prevent the occurrence and development of infection [4, 11, 12].

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In the treatment of diabetic wounds, biological dressings have many significant advantages over traditional treatments. In a controlled study, the proportion of patients who used bioengineered skin substitutes to complete wound closure within 4 and 6 weeks was 85% and 95%, respectively, which was significantly higher than that of patients who received standard treatment (30% and 35%), indicating that the substitutes can promote wound closure and make the healing of chronic diabetic ulcers faster and more consistent. [13] . In addition, by providing scaffolds or carriers, biodegradable materials combined with various active substances or cells help promote diabetic wound healing. These materials not only show strong biocompatibility, but also actively intervene in the immune response during wound healing, promote angiogenesis, accelerate skin cell proliferation and re-epithelialization, and regulate collagen remodeling, thereby inhibiting scar hyperplasia [14].

In recent years, the rapid development of biomedical materials science has provided new ideas and means for diabetic wound management. Among them, biological dressings, as a new kind of material with excellent biocompatibility, degradability, and ability to promote tissue repair, have shown great potential in promoting wound healing. This article first introduces the healing process of normal wounds and the effects of diabetes on the body, which lead to diabetic wounds that are susceptible to infection and infected wounds that are difficult to heal. In addition, we also comprehensively analyzed the mechanism and effect of these three most commonly used biological dressings (hydrogel, fiber scaffold, microneedle patch) in promoting diabetic wound healing, inhibiting infection, promoting body immunity, regulating inflammatory response, and reviewed the latest application progress of the three biological dressings in the treatment of diabetic infected wounds. Finally, the current challenges and future research directions of biological dressings in the treatment of diabetic-infected wounds are proposed.

2. Formatting the title, authors and affiliations

Normal wound healing is a complex process, which mainly includes four periods of hemostasis, inflammation, proliferation, and remodeling [15]. When trauma occurs, platelets will overflow from the ruptured blood vessels, and platelets and complex coagulation cascades are activated, including the stepwise activation of a variety of serine proteases, leading to the cleavage of fibrinogen into thrombin of fibrin and the formation of fibrin fibers, forming a reticular clot to seal the defect and achieve preliminary hemostasis [16]. After that, the inflammatory cascade is activated, and neutrophils, macrophages, and lymphocytes respond to injury signals and are recruited from the circulation to the wound microenvironment in a specific spatiotemporal order, starting to phagocytose bacteria and dead tissue debris and secrete growth factors [17]. In the subsequent proliferative phase, macrophages and injured endothelial cells release FGF-2、VEGFA, Promoting angiogenesis [18, 19]. Capillary sprouts infiltrate the injured site, form granulation tissue with fibroblasts and immune cells, and provide nutrition and oxygen for cell metabolism [20]. Growth factors such as EGF and TGF-β stimulate the proliferation and migration of keratinocytes at the edge of injury and re-epithelialization of the injured dermis [21]. At the final remodeling stage, keratinocytes stop proliferating and migrating and begin to differentiate. The granulation tissue formed in the early repair process undergoes internal transformation, which is gradually replaced by the new collagen-rich dermal matrix and gradually transformed into mature scar tissue [1].

In contrast, in the wound healing process of diabetic patients, the wound inflammatory response is often excessive and lasts longer, which may be due to the impaired immune function and imbalance of inflammatory regulation caused by hyperglycemia [22]. In addition, the hyperglycemic environment inhibits the proliferation and migration of fibroblasts, and reduces collagen synthesis and angiogenesis, resulting in slow granulation tissue formation and delayed wound contraction and epithelialization process [23]. Moreover, diabetic wound healing is often accompanied by excessive collagen deposition, but the arrangement is disordered, resulting in low strength and poor elasticity of the healed tissue, which makes it easy to form irregular scars [22]. At the same time, diabetic wounds are often infected, further hindering healing, because hyperglycemia provides a good growth environment for bacteria, and the decline of immune function in diabetic patients makes the wound more susceptible to infection [24].

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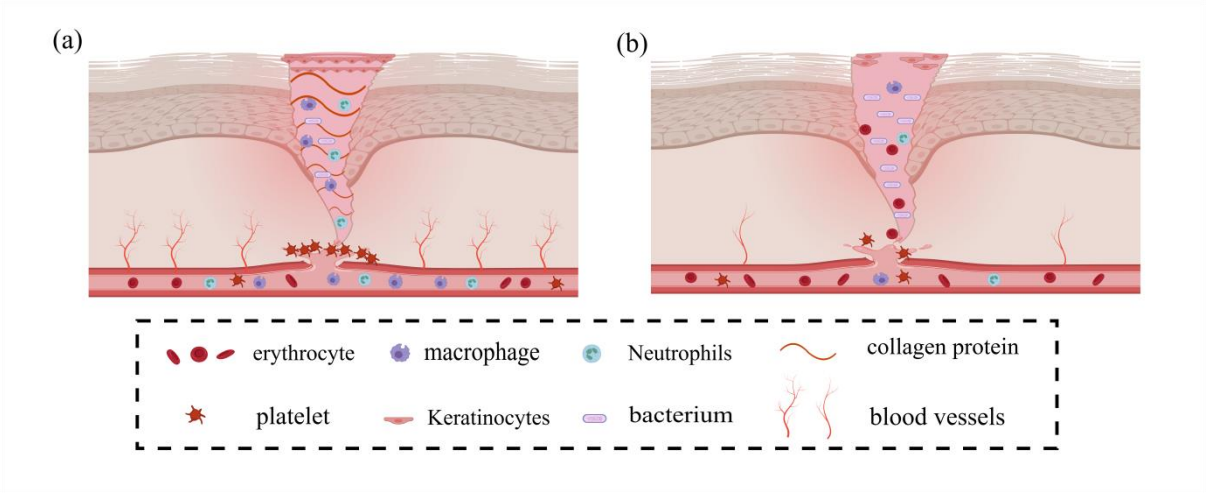

Figure 1. Comparison of normal wound and diabetic wound. **a** normal wound **b** diabetic wound

3. Mechanism of diabetes inhibiting wound healing

Unlike normal wounds, which heal quickly and have little pain, diabetic-infected wounds heal difficultly and take a long time, ranging from dozens to hundreds of days, and their complexity and potential lethality are significantly increased [25]. The consequences of diabetic foot ulcer (DFU) include decreased functional status, infection, hospitalization, lower limb amputation, and death [26]. According to a recent report, The 1-year mortality rate was 13.1%, the 5-year mortality rate was 49.1%, and the 10-year mortality rate was 76.9% after the DFU event. Cardiovascular disease and infection were the main causes of death [27]. It can be seen that diabetes has a very serious impact on the healing of infected wounds, and the risk of death is high. Next, this article will deeply analyze how diabetes inhibits wound healing by affecting immune system function, cell function, metabolic function, and other aspects.

3.1. Immune system dysfunction

Diabetes, as a global public health challenge, its complications are not only limited to the classic microvascular and macrovascular lesions but also profoundly affects the immune response and repair mechanism of the body, especially for the healing process of infectious wounds [28-30]. The imbalance of immune regulation under this pathological condition leads to the persistence of a chronic inflammatory state and slows down the healing of infected wounds, which involves the disorder of multiple immune cell functions and the tilt of cytokine balance.

3.1.1. Immune cell dysfunction. The characteristic hyperglycemic state of diabetes has a profound impact on the multifaceted functions of the host immune system [5, 7]. Especially the key groups involved in infectious wound defense, such as macrophages, neutrophils , NK cells, T cells, and B cells, their functions are significantly inhibited, and the chemotaxis, phagocytic capacity, and bactericidal efficacy of these cells are decreased, which directly hinders the effective removal of pathogenic microorganisms in the wound and significantly hinders the normal process of wound repair.

3.1.1.1. Macrophages. Macrophages, as professional antigen-presenting cells, play a role in infection by phagocytosis, secretion of cytokines, and presentation of antigens to T cells. When the blood glucose level increases, it may lead to the impairment of immune system function, thus affecting the normal function of macrophages. For example, under hyperglycemia, the phagocytic capacity and antigen-presenting function of macrophages may be inhibited, which will affect the activation of T cells and the production of effector cells [31]. In addition, oxidative stress and accumulation of advanced glycation end products triggered by hyperglycemia significantly inhibited the normal polarization process of macrophages, resulting in sustained activation of M1 macrophages, while the conversion of M2

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macrophages to repair phenotype was blocked. M1 and M2 macrophages play different roles in inflammation and tissue repair. M1 macrophages are mainly responsible for the initial inflammatory response, clearing invading pathogens and necrotic tissues, while M2 macrophages participate in the subsequent tissue reconstruction and repair process, promoting angiogenesis and granulation tissue formation [32, 33]. So, Excessive activation of M1-type macrophages may lead to tissue damage and inflammation, The blocked transition of M2 macrophages to repair phenotype is not conducive to tissue repair and regeneration [32, 34]. This m1/m2 imbalance not only aggravates the local inflammatory state of the wound but also inhibits the necessary tissue repair and regeneration process, prolongs the healing time, and reduces the healing quality.

3.1.1.2. Neutrophils. The number of neutrophils in the wound of diabetic patients increases, but its function shows a "paralyzed" state, which is mainly caused by the abnormal formation of nets (neutrophil extracellular trap net) and the decrease of membrane lipid fluidity. First, the formation of neutrophil nets is significantly increased in the diabetic state [35]. Nets are important roles of neutrophils in the defense during the initial stage of infection, and they can capture and eliminate pathogens [36]. However, excessive or persistent nets can lead to delayed the wound healing ability of diabetic foot ulcers, which indicates that the abnormal formation of nets reduces the healing ability of diabetic patients [35]. On the other hand, neutrophils in diabetic patients have decreased membrane lipid fluidity and increased membrane microviscosity, which may be caused by long-term hyperglycemic state and enhanced lipid peroxidation [37, 38]. These changes directly lead to the decline of bacterial clearance ability at the wound site, increasing the risk and severity of infection.

3.1.1.3. Natural Killer Cells. Natural killer cells (NK cells) as a key component of the early immune response against pathogens, their cytotoxicity is attenuated in diabetes, while the number and activity of NK cells are also significantly reduced, resulting in insufficient immune response against infection [39-41]. Hyperglycemia inhibits the cytotoxic effect of NK cells through a variety of ways, which significantly reduces the degranulation ability of NK cells, including reducing the expression and release of perforin and granzyme B, thereby weakening the clearance ability of bacteria and damaged cells at the wound and prolonging the infection state [42]. During wound healing, An appropriate inflammatory response mediated by NK cells is essential to initiate the healing process. Its dysfunction may lead to weak or strong local inflammation of the wound, affecting the release of growth factors and cell migration, thereby delaying the healing process [43, 44]. In addition, NK cells and other immune cells (such as macrophages T cell) interactions are impaired in diabetes, interfering with immune cell coordination required for wound healing, and affecting tissue remodeling and regeneration [45].

3.1.1.4. T cells. Diabetes affects the regulatory function of T cells TCR signaling, chronic inflammatory state, and T cell aging. The study found that the suppressive resistance of effector T cells (teff) from T1D patients to Tregs is enhanced [46]. In addition, the proportion and function of regulatory T cells are reduced in patients with type 2 diabetes mellitus (T2DM) [47]. The function of regulatory T cells is impaired and cannot effectively inhibit excessive inflammatory response, resulting in the persistence of a chronic inflammatory state at the wound, affecting granulation tissue formation and epithelial regeneration, and delaying the healing process [22]. In addition, high glucose levels promote the differentiation of regulatory T cells and inhibit the differentiation of Th1 effector T cells, which tend to Th2 response, which may inhibit the effective anti-bacterial immune response, prolong the inflammatory period of infected wounds, and hinder healing [48]. On the other hand, T cells in T1D drive autoimmune disease, Abnormalities in TCR signaling affect many aspects of cd4+ and cd3+ T cells, including thymus development, peripheral homeostasis, effector subset differentiation function, and memory formation [49]. This will weaken the ability of T cells to respond to antigen again, which will not only affect the clearance of primary infection but also may lead to repeated wound infection and hinder the healing process. Moreover, abnormal T cell function promotes the formation of a local chronic inflammatory environment of the wound. Excessive secretion of inflammatory cytokines, such as TNF-α and IL-6,

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stimulates fibroblast proliferation, leads to excessive fibrosis, and affects the quality of wound healing [22]. Finally, There are more senescent T cells in T2DM patients, and these senescent T cells are accompanied by increased levels of systemic inflammation, which adversely affects immune function [50].

3.1.1.5. B cells. The hyperglycemic environment has a significant impact on the maturation, differentiation, and function of B cells, reduces the resistance of diabetic patients to infection, prolongs wound healing time, and may lead to a chronic inflammatory state. First, the hyperglycemic environment inhibits the mature differentiation of B cells and reduces the number of anti-infectious antibodies (such as IgG,IgM) production and quality, reduces the clearance efficiency of wound infection, increases the duration and severity of infection, and prolongs the healing time [51]. In addition, the production of ROS and accumulation of advanced glycation end products by diabetes-related oxidative stress can impair the antibody diversity of B cells, limiting the comprehensive response to pathogens [52, 53]. Studies have shown that B cells in diabetic patients perform poorly in humoral immunity, and their immune regulatory functions are impaired, including the ability to secrete cytokines (such as IL-10) and participate in immune regulation as antigen-presenting cells [54]. The decline of these immune functions not only affects the resistance of diabetic patients to infection, but also may lead to a chronic inflammatory state, which may lead to the abnormal activation of autoreactive B cells, and then produce autoantibodies that attack neovascularization or other cells, which will inhibit tissue repair [55].

3.2. Impaired cell function and proliferation

The healing ability of diabetic patients to infected wounds is much lower than that of non-infected wounds, because of the impairment of the function of key healing cells, especially those involved in tissue repair and regeneration. The following article will explain the impact of diabetes on the function and proliferation of key cells such as fibroblasts, endothelial cells and keratinocytes, which significantly weaken the body's ability to promote the healing of infected wounds.

3.2.1. Fibroblasts. Fibroblasts, as the main effector cells in wound healing, are responsible for collagen synthesis and remodeling and are essential for the recovery of wound strength [68, 69]. In the diabetic and infected wound environment, sustained hyperglycemia, oxidative stress and fighting with persistent bacteria or toxins greatly damage the viability of fibroblasts, inhibit their proliferation and migration, and lead to the imbalance of extracellular matrix (ECM) deposition, reduce the maturation and cross-linking of collagen, thus delaying the wound closure process. In addition, fibroblasts from diabetic patients exhibit excessive response to pro-inflammatory factors, which exacerbate the inflammatory state and further hinder the healing process [8].

3.2.2. Endothelial cells. As the basic unit of blood vessels, endothelial cells' functional status directly affects the blood supply and oxygen supply in the infected wound area [70].A hyperglycemic environment can lead to oxidative stress in vascular endothelial cells and reduce the bioavailability of nitric oxide (no) [71]. No is an important vasodilator. Its reduction will aggravate vasoconstriction and reduce blood flow, which not only affects the blood supply and oxygen delivery at the infected wound but also reduces the effective transport capacity of immune cells required to fight infection [71]. What is more worrisome is that hyperglycemia also inhibits the immune defense mechanism mediated by endothelial cells, including reducing the phagocytic capacity of leukocytes and reducing the production of growth factors and antimicrobial peptides, which weaken the ability of wounds to resist bacterial infection. Diabetic wounds are prone to infection and heal slowly, partly due to the local immunosuppressive state caused by endothelial cell dysfunction [31, 72, 73]. In addition, damaged endothelial cells are more likely to make bacteria penetrate the vessel wall, promote the spread of local infection, further destroy the microenvironment of neovascularization, and form a vicious circle of healing. In addition, diabetic patients' microvascular lesions lead to capillary basement membrane

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thickening, vascular permeability changes and increased thrombophilia, which will limit the normal function of endothelial cells [72].

3.2.3. Keratinocytes. As the main component of the epidermal layer, keratinocytes not only constitute a physical barrier but also play a central role in regulating the inflammatory response and promoting epithelialization [74, 75]. Under diabetic conditions, the proliferation and migration ability of keratinocytes is impaired, and the effect of advanced glycation end products on their membrane proteins leads to the impairment of cell-cell adhesion and signal transmission, delaying the completion of epithelial coverage [76]. In addition, during the regeneration process of an infected wound surface, keratinocytes not only need to quickly cover the wound surface to prevent microbial invasion but also need to work together with inflammatory cells to clear the infection. However, diabetes slows down the migration speed of keratinocytes, weakens their barrier function, and affects tight junctions and signal transmission between cells, making infection difficult to effectively control and prolonging the recovery time of epidermal integrity [77-79].

Table 1. Effects of diabetes on different cells.

Cell species	Effects of diabetes on cells	Wound manifestations of diabetic infection	Res.
Macrophage	Impaired phagocytosis, impaired antigen-presenting function, and m1/m2 imbalance (M1 type macrophages are continuously activated, while M2 type macrophages are blocked from switching to a repair phenotype.)	The local inflammatory state of the wound is aggravated, the inhibition of the necessary tissue repair and regeneration process is inhibited, the wound healing time is prolonged and the healing quality is reduced.	[31-34]
Neutrophils	The formation of nets increased significantly, the fluidity of membrane lipids decreased, and the membrane microviscosity increased.	The wound infection was aggravated and the healing was delayed.	[35,37,38]
NK cells	The number and activity of NK cells were significantly reduced, the cytotoxicity was decreased, the degranulation ability was significantly reduced, and the appropriate inflammatory response mediated by NK cells was abnormal.	The state of wound infection is prolonged, affecting tissue remodeling and regeneration.	[39-44]
T cells	The proportion and function of regulatory T cells are reduced, the differentiation of regulatory T cells is strengthened, and the differentiation of Th1 effector T cells is inhibited, which tends to Th2 response, cd4+ and cd3+ T cell function is impaired, and aging T cells are increased.	The primary infection is difficult to remove, the wound is repeatedly infected, the chronic inflammatory state persists, affecting granulation tissue formation and epithelial regeneration, excessive fibrosis, delaying the healing process, and the quality of wound healing is poor.	[22,47-50]

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Table 1. (continued)

B cells	It inhibits the maturation and differentiation of B cells, reduces the production and quality of anti-infection antibodies, and impairs the immune regulatory function.	The duration and severity of wound infection increased, and the healing time was prolonged.	[51-54]
Fibroblasts	Viability was weakened, proliferation and migration were inhibited, and extracellular matrix (ECM) deposition was imbalanced.	The maturation and cross-linking of collagen at the wound were reduced, and wound healing was delayed.	[68,69]
Endothelial cells	Oxidative stress occurs, cell structure is damaged, and the immune defense mechanism mediated by endothelial cells is inhibited	The infection at the wound is aggravated, the local infection may spread, the vascular synthesis is blocked, and the wound healing is slow.	[31,71-73]
Keratinocytes	Impaired proliferation and migration, cell-cell adhesion and signal transmission.	The wound infection is difficult to control and the wound healing time is prolonged.	[76-79]

3.3. Metabolic disorder

In diabetic patients, metabolic abnormalities are not only limited to the imbalance of blood glucose regulation but also involve the widespread disorder of energy, protein metabolism and redox status. These factors act on the microenvironment of infectious wounds, resulting in delayed healing and increased risk of infection.

3.3.1. Energy metabolism disorder. Diabetic patients have insulin resistance and insulin secretion defects, which lead to glucose utilization disorders and limited intracellular energy production [9]. In infectious wounds, abnormal energy metabolism leads to reduced ATP production, affecting cell proliferation, migration and extracellular matrix synthesis, and delaying wound healing [80]. In addition, the high glucose environment promotes the glycolytic pathway rather than aerobic oxidation, exacerbates lactate accumulation, further worsens the wound microenvironment, and hinders immune cell function [81, 82].

3.3.2. Protein metabolism disorder. Protein is the basis of cell structure and function and is essential for new tissue generation and wound repair. Abnormal protein metabolism directly affects the quality and speed of wound healing. Due to the enhanced gluconeogenesis, the protein decomposition and synthesis in diabetic patients are accelerated, resulting in negative nitrogen balance, physical strength, and weight loss [83, 84]. Hyperglycemia inhibits the protein synthesis of fibroblasts, endothelial cells, and immune cells through the accumulation of advanced glycation end products (AGEs), the activation of protein kinase C (PKC), and the increase of oxidative stress, especially the decreased synthesis of collagen, growth factors, and cytokines, affecting extracellular matrix remodeling and immune defense, especially the reduction of protein synthesis related to collagen synthesis, antimicrobial peptides and immunoglobulins, directly weakening the physical barrier function of the wound and the antibacterial ability of the body, and prolonging the healing time of infectious wounds [85].

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3.3.3. Redox state disorder. The hyperglycemic environment promotes the generation of free radicals, exceeding the scavenging capacity of the body's antioxidant defense system, resulting in oxidative stress [86]. Oxidative stress not only damages cell structure, such as DNA, protein, and cell membrane, but also affects cell signaling, interferes with the normal healing process, makes infectious wounds more difficult to heal, and may aggravate the inflammatory response [87, 88].

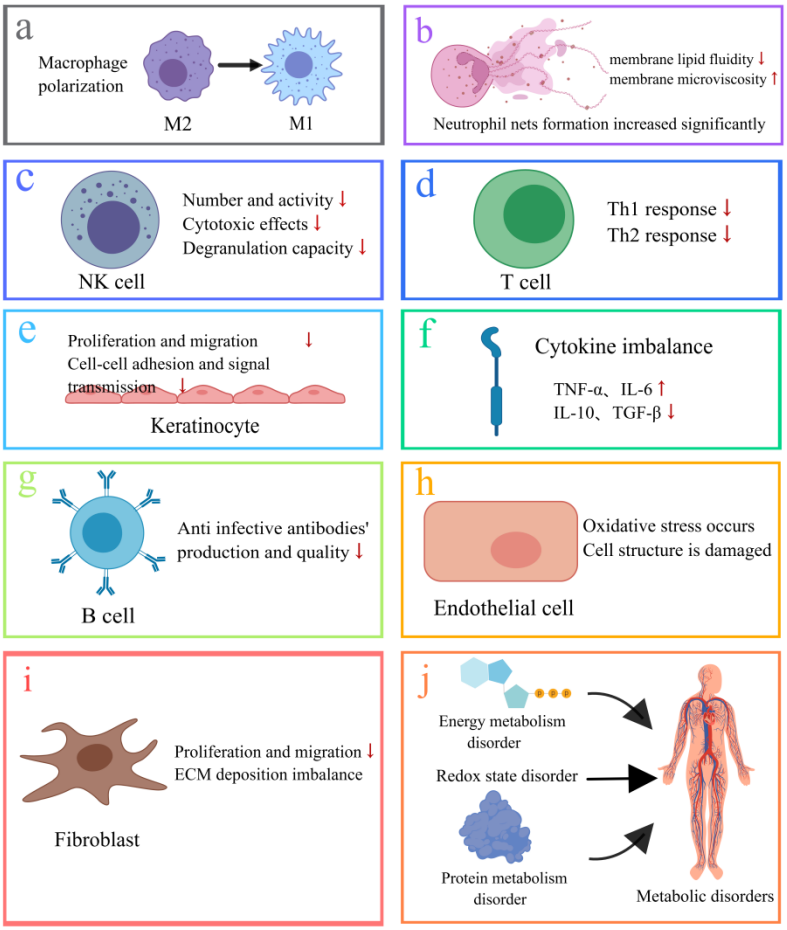

Figure 2. The mechanism of diabetes making wounds difficult to heal. **a** M1 macrophages are continuously activated, while M2 macrophages are blocked from switching to a reparative phenotype. **b** Neutrophil net formation increased significantly, membrane lipid fluidity decreased, and membrane microviscosity increased. **c** NKThe number and activity of NK cells were significantly reduced, the cytotoxicity was decreased, and the degranulation ability was significantly reduced. **d** Inhibited the differentiation of Th1 effector T cells and tended to Th2 response. **e** Inhibit the maturation and differentiation of B cells,and reduce the production and quality of anti-infection antibodies. **f** Cytokine imbalance, increased levels of TNF- α and IL-6, and decreased levels of IL-10 and TGF- β. **g** Fibroblast proliferation and migration were inhibited, and extracellular matrix (ECM) deposition was imbalanced. **h** Endothelial cells produce oxidative stress and cell structure is damaged. **i** Impaired proliferation and migration of keratinocytes, impaired cell-cell adhesion and signal transmission. j Metabolic disorder (energy metabolism disorder, protein metabolism disorder, redox state disorder)

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4. Biological dressings for the treatment of diabetic-infected wounds

4.1. Hydrogels

4.1.1. Conventional hydrogels. Hydrogels are hydrophilic, three-dimensional, and cross-linked polymer networks capable of absorbing approximately 10-20 times their initial weight of water or biological fluids [90]. The protective layer formed by hydrogel can prevent external pollutants from invading the wound again, while keeping the wound moist, which is conducive to tissue regeneration and healing, and reduces scar formation. Hydrogels have been used as wound dressings due to their tissue-like softness and biocompatibility [91]. Wounds of diabetic patients are usually infected with biofilm bacteria, which are characterized by high oxidative stress [92]. Therefore, hydrogels used to treat diabetic-infected wounds generally have antibacterial and antioxidant properties. Y. Lin et al developed a non-crosslinked chitosan (CS) / hyaluronic acid (HA) hybrid hydrogel, which showed broad-spectrum antibacterial activity and the ability to promote fibroblast proliferation and migration, while having excellent reactive oxygen species (ROS) scavenging ability and cytoprotection under oxidative stress [93]. In addition, some hydrogels can regulate the expression of growth factors in the human body. C. Xing et al designed a chiral gel dressing (HA-LM2-RMR) composed of helical nanofibers co-assembled with L-phenylalanine and cationic hexapeptide, which were crosslinked with hyaluronic acid through hydrogen bonding. This dressing can not only effectively reduce advanced glycation end products (AGEs), but also specifically kill multidrug-resistant bacteria. In addition, it can activate sprouting angiogenesis of human umbilical vein endothelial cells by upregulating the expression of VEGF and OPA1 and shorten the healing period from 21 days to 14 days [94].

4.1.2. Drug-loaded hydrogels. To further regulate the wound microenvironment, control infection, and promote wound healing, many researchers loaded a variety of substances on hydrogels, such as antibiotics, nanoparticles, growth factors, glucose oxidase, nanoenzymes, and oxidants, to promote the healing of infected wounds.The hydrogel loaded with antibiotics can control the release rate of antibiotics, realize the long-term continuous supply of drugs at the treatment site, reduce the development of bacterial resistance to antibiotics, and reduce systemic toxic and side effects. At the same time, it can more accurately act on pathogens, improve the local antibacterial effect, and accelerate the healing process of infected wounds. T. Khaliq et al. hydrogel dressing based on keratin pullulan was loaded with cefotaxime sodium (CTX), which made CTX release controlled. The dressing group had fast wound closure, obvious angiogenesis, accelerated re-epithelialization, and more collagen deposition at the wound site [6]. Mengjing Fu et al. developed a double crosslinked interpenetrating polymer network hydrogel with antibiotic gentamicin (Gen) as a dynamic crosslinking agent, which can achieve pH-responsive drug release in the microenvironment of the infection site and enhance the mechanical properties of the hydrogel. Moreover, the drugs in the hydrogel can achieve sustainable release, and the antibacterial activity against gram-positive bacteria (Staphylococcus aureus) and gram-negative bacteria (Escherichia coli) can be maintained for more than 28 days, accelerating wound healing [95].

Hydrogels loaded with metal nanoparticles can solve infections caused by antibiotic-resistant bacteria. Silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), and copper nanoparticles (CuNPs) are all antibacterial metal nanoparticles that can promote wound recovery. Among the above nanoparticles, AgNPs are the most active nanoparticle to promote wound healing because of their antibacterial effect on natural and multidrug-resistant microbial strains [96]. Reena Badhwar et al. prepared a hydrogel matrix (QCT-AgNPs) containing quercetin silver nanoparticles. The study showed that compared with the commercially available gel, QCT-AgNPs hydrogel is more effective against Staphylococcus aureus and Escherichia coli, significantly reduces the wound gap, and increases the percentage of re-epithelialization [97]. H. Meng et al. Incorporated chitosan functionalized gold nanoparticles into hydrogel dressing (Gel/CS-AuNPs) and formulated it through chemical crosslinking of gelatin and sodium alginate. In diabetic wound model rats, Gel/CS-AuNPs effectively killed MRSA,

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reduced inflammation, and promoted angiogenesis and collagen deposition and remodeling at the wound site [98].

Growth factors are a class of protein or polypeptide molecules that can stimulate cell proliferation, migration, differentiation, and survival [99]. Hydrogels loaded with growth factors can reduce the frequent dependence on exogenous antibacterial agents, promote tissue repair and regeneration, and promote wound healing. Peiyu Yan et al. introduced platelet-rich plasma (PRP), which can release a variety of growth factors, into the hydrogel formed by the conjugate addition of natural antibacterial poly amino acid ε-poly lysine (ε-PL) and methacrylate gelatin, which not only enhanced the mechanical strength of the hydrogel, but also maintained its antibacterial efficacy. The combination of PRP and ε-PL confirmed the enhanced antibacterial properties and promoted the growth of human umbilical vein endothelial cells [100]. Yining Chen et al. loaded the anti-inflammatory acetyl-11-keto -β- boswellic acid (AKBA) of medicinal plants into hyaluronic acid-based micelles(MIC@AKBA), encapsulated in hydrogels together with basic fibroblast growth factor (bFGF), which promotes wound healing by reducing inflammation and oxidative stress while accelerating angiogenesis [101].

4.1.3. Stimuli-responsive hydrogels. Diabetic infected wounds have a special microenvironment, such as hyperglycemia pH changes, etc., which makes hydrogels with stimuli-responsive structures respond to changes in the wound microenvironment (pH, enzymes, reactive oxygen species, and glucose), thereby releasing active substances and making diabetic wounds heal faster.

Diabetic wounds are often accompanied by an acidic microenvironment (pH reduction), the pH-responsive hydrogel can adjust the drug release rate according to the change of wound pH. The design of such hydrogels usually involves acid-sensitive groups, such as carboxymethyl cellulose, polyacrylic acid, etc. They change their structure in an acidic environment, control the release of drug loads, effectively inhibit bacterial growth, and promote cell proliferation. Cui Cheng et al. ε-poly-I-lysine grafted graphene quantum dots and benzaldehyde terminated four-arm polyethylene glycol were used as materials to form hydrogels in situ through dynamic imine bond crosslinking. The hydrogels can respond to the acidic environment triggered by bacteria, exert the synergistic effect of chemotherapy and xenon light irradiation, lead to bacterial membrane rupture and bacterial inactivation, promote the migration and proliferation of fibroblasts, enhance the adhesion of platelet endothelial cells, and ultimately accelerate the healing of infected diabetic wounds [102]. Cheng Hu et al. developed a multifunctional double crosslinked hydrogel by Schiff reaction between catechol adducts and amino groups (-NH2) in chitosan quaternary ammonium salt (HTCC) and aldehyde groups (-CHO) in oxidized dextran dopamine (OD-DA). The double Schiff base bonds in hydrogels can rapidly achieve pH response and achieve sustained and controlled release of drugs to accelerate wound healing. Through the effective encapsulation of AgNPs and the pro-angiogenic drug deferoxamine (DFO), the hydrogel has antibacterial and angiogenic properties [103].

Using the thermosensitive property, the temperature-responsive hydrogel can change its swelling degree and drug release characteristics under local heating (such as near-infrared light irradiation) or body temperature stimulation. This strategy is especially suitable for the treatment of deep wounds. By accurately regulating drug delivery, it can enhance the therapeutic effect and reduce the damage to surrounding healthy tissues. Zhe Lu et al. prepared hydrogels by digital light processing (DLP) 3D printing a mixture containing N-isopropylacrylamide (NIPAm), curcumin loaded Pluronic F127 micelles (Cur-PF127) and poly (ethylene glycol) diacrylate dopamine (PEGDA575-Do). The thermoresponsive backbone (polymerized NIPAm) can activate wound contraction through body temperature, which helps accelerate the healing of diabetic wounds infected with methicillin-resistant Staphylococcus aureus (MRSA) [104]. Zexiang Zheng et al. prepared CeO2NPs with photothermal conversion ability, which can be used as a photothermal agent to endow the hydrogel with photothermal conversion ability with the help of a near-infrared laser. The nanoparticles were pre-embedded in the thermosensitive gel and then compounded in the SA hydrogel network. In cellular studies, hydrogels showed the temperature-responsive release of CeO2NPs, significant antibacterial and antioxidant

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activities, and the ability to remove and promote the healing of infected diabetic wounds without damage, with low cytotoxicity [105].

Given the continuous hyperglycemia in diabetic patients, glucose-responsive hydrogels react with glucose through glucose-sensitive elements (such as glucose oxidase), triggering drug release or material degradation, achieving dynamic response to the wound microenvironment. This kind of hydrogel can not only provide necessary therapeutic substances but also serve as a tool for blood glucose monitoring. Wei Zhu et al. designed a smart hydrogel dressing composed of 3, 3', 5, 5'-tetramethylbenzidine/ ferrousion/ Pluronic F-127/ glucose oxidase (TMB/Fe2+/PF127/GOx). The loaded GOx degraded blood glucose to provide hydrogen peroxide (H2O2) and gluconic acid to support the Fe2+ - based Fenton reaction and the generated hydroxyl group promoted the oxidation of TMB, which could visually monitor the colorless to green color change caused by TMB oxidation in 1 to 10 mm blood glucose. Meanwhile, chemokinetic therapy (CDT) is induced to kill bacteria by generating specific hydroxyl radicals [106]. Xingchen Li et al. synthesized hydrogels using copper nanoclusters (CuNCs) crosslinked in situ with oxidized hyaluronic acid (HA-ALD) and modified with glucose oxidase (GOx). GOx enzymatically degrades excess glucose at the wound site, producing gluconic acid and H2O2, CuNCs can catalyze the generation of reactive oxygen species (ROS) by degrading H2O2 through Fenton reaction to eradicate drug-resistant bacteria. In addition, CuNCs endow hydrogels with excellent conductivity and can promote blood vessel formation by electrical stimulation, thus promoting tissue repair around the wound area [107].

ROS-responsive hydrogels, which contain antioxidants or ROS scavengers, are released when ROS levels are detected to increase, effectively alleviating oxidative stress and promoting wound healing. Polymer chains containing antioxidant groups, such as thiosulfate and vitamin E derivatives, are usually used in the design. Ya Guan et al. proposed a sustained oxygenation system consisting of oxygen-releasing microspheres and reactive oxygen species (ROS) - scavenging hydrogels. Hydrogels capture naturally elevated ROS in diabetic wounds, allowing microspheres to release oxygen. The sustained release of oxygen increases the survival and migration of keratinocytes and dermal fibroblasts, promotes the expression of angiogenic growth factors and angiogenesis in diabetic wounds, reduces the expression of proinflammatory cytokines, and increases the wound closure rate [108].

4.2. Fiber scaffolds

In recent years, fiber scaffolds have attracted extensive attention in the field of promoting wound healing of diabetic infections due to their unique structure and tunable biological activity. This article focuses on several innovative strategies, including drug loading, antibacterial performance improvement, angiogenesis promotion, antioxidant stress, and cell regulation.

Manjit Manjit et al. prepared gelatin-coated PCL nanofibers by electrospinning technology and realized the synergistic loading of luliconazole and naringenin. The biocompatibility and biodegradability of PCL combined with the hydrophilicity and adhesion of gelatin optimized the bio-interface properties of nanofibers and improved the drug delivery efficiency. In vitro and in vivo studies have shown that the nanofibers can effectively inhibit fungal biofilms and promote rapid wound healing [109]. Lei Yin et al. developed a dressing that is both antibacterial and pro-angiogenic by encapsulating dimethyloxalylglycine (DMOH) in zeolite imidazolate framework (ZIF-8) and integrating it into gelatin polycaprolactone (Gel-PCL) nanofibers. The degradation of ZIF-8 timely released zinc ions and DMOG effectively inhibited bacterial infection and accelerated the healing process of skin wounds in diabetic rats [110].

Haibing Liu et al. designed to integrate mupirocin and cerium oxide nanoparticles into polyvinyl alcohol chitosan (PVA/CS) nanofibers to develop a multifunctional dressing that can remove ROS and effectively inhibit bacteria. This dressing not only shows high-efficiency inhibition against a variety of bacteria but also maintains the balance of local ROS levels and promotes the stability of the wound-healing environment [111].

Z. Wang et al. successfully prepared a series of Quaternary chitin (QC) and fibroblast growth factor 2-hyaluronic acid (FGF2-HA) - modified poly (lactic co glycolic acid) (PLGA) nanofiber dressings. The

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dressing has broad-spectrum antibacterial activity and promotes the proliferation and migration of L929 cells by activating the cell cycle and epithelial mesenchymal transition (EMT) pathway. The wound model results of MRSA infection showed that the dressing promoted wound healing within 15 days mainly by reducing inflammation, enhancing collagen deposition, and promoting proliferation and vascularization [112].

4.3. Microneedle patches

In recent years, microneedle technology, as an important branch of the drug delivery system, has shown great potential in the field of non-invasive treatment due to its unique transdermal drug delivery method. Microneedle patches directly deliver drugs to the target site through micro channels on the skin surface, bypassing the skin barrier, reducing the first-pass effect of drugs, and improving the bioavailability [23]. This feature makes microneedle technology show unique advantages in the treatment of diabetic infected wounds, especially in the local precise delivery of antibiotics, nanoparticles, growth factors, enzymes, and even stem cells, in order to control infection, regulate the immune system, and promote tissue repair.

Asad Ullah et al. constructed an intelligent delivery system based on pH-responsive polymer-coated microneedles. By coating a layer of Eudragit S100 film on the surface of the microneedle, which is sensitive to pH and only dissolves at a higher pH value (pH 7.5) that mimics the wound environment, the model drug encapsulated in the porous polymer film is automatically released. This ensures that the drug is released only when needed, reducing side effects and improving treatment efficiency. The porous layer on the microneedle uses aqueous gelatin as porogen, which not only increases the drug loading but also promotes the effective diffusion of drugs in the wound site, helping to penetrate the biofilm and necrotic tissue barrier. The experimental results showed that the microneedle device exhibited rapid responsive release characteristics to the pH of the wound environment, while there was almost no drug leakage under normal skin pH [113].

Shengbo Li et al. developed an innovative microneedle patch system (PFG/MN), The core design of the PFG/MN system lies in the tip of microneedles, where the complex of polydopamine (PDA) - loaded iron oxide nanoparticles with glucose oxidase (GOx) and hyaluronic acid (HA) (Fe/ PDA@GOx @HA). When the microneedles penetrate the biofilm on the wound surface, Fe/ PDA@GOx @HA is released into the infected environment and subsequently decomposed under specific microenvironment stimuli (such as high glutathione and low pH) to release active ingredients. GOx catalyzes the conversion of glucose and generates hydrogen peroxide, while PDA exerts a photothermal effect under laser excitation. The synergistic effect of the two not only enhances the chemical kinetics and photothermal antibacterial effect but also promotes the polarization of M2 macrophages in the wound environment, which is conducive to tissue repair. In addition, amine-modified mesoporous silica nanoparticles (AP-MSN) are incorporated into the base of microneedles, which can further promote wound healing by capturing and scavenging pro-inflammatory factors, such as free nucleic acids, in the wound, thereby regulating the immune response [114].

Jingjing Gan et al. introduced a kind of adhesive microneedle (MN) patch integrating mesenchymal stem cell-derived exosomes (MSC-expos) and antibacterial silver nanoparticles (AgNPs) with spatiotemporal changes. Its porous methacrylate gelatin hydrogel tip can release MSC-exposed to the depth of the wound on demand. These exosomes are rich in bioactive molecules that promote healing, which can effectively anti-inflammation, promote angiogenesis, accelerate cell function recovery, vascular remodeling and immune system reconstruction. The back of the patch adopts natural silk fibroin material, which not only ensures good skin adhesion without additional bandaging but also provides a long-lasting antibacterial barrier by incorporating AgNPs, effectively resisting microbial invasion and further promoting wound healing [115].

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Table 2. Advantages and disadvantages of various biological dressings.

Biological dressing	Advantage	Shortcoming	Refs.
Hydrogels	High biocompatibility and moisture retention.	Low mechanical strength, easy to fall off, wet environment may increase the risk of infection of diabetic wounds, drug release is difficult to control, and the cost is high.	[102-108]
Fiber scaffolds	It can carry drugs, growth factors, nanoparticles, etc., for local drug delivery	Foreign body reaction and thickness affect revascularization, and the production cost is high.	[109-112]
Microneedle patches	It can respond to pH, enzymes, reactive oxygen species and glucose, and improve the accuracy and efficiency of treatment.	Different individuals may affect microneedle penetration efficiency, potential skin irritation or infection risk, not all drugs are suitable for delivery through microneedle patches.The cost is high.	[113-115]

5. Challenges and future prospectives

Although biological dressings have shown great potential in the treatment of diabetic infectious wounds, they still face severe challenges. The primary difficulty lies in infection control and immune regulation. Diabetic patients with impaired immune function due to hyperglycemia are prone to concurrent infection and slow wound healing. This requires that biological dressings need to have high-efficiency antibacterial properties to control infection, and also need to have the ability to regulate the immune response, promote the restoration of the immune balance of damaged tissues, and avoid excessive inflammatory reactions hindering wound healing. In addition, the lack of personalized treatment strategies is also a major bottleneck. Given the variability of wounds in different patients, there is an urgent need to develop customized biological dressing solutions that can target individual differences, wound stages, and locations. At the same time, the optimization of biocompatibility and biodegradability should not only ensure the good coordination between the material and the host, but also finely regulate the degradation rate to avoid adverse reactions, which is another key factor improving the clinical efficacy.

Looking forward to the future, the research of biological dressing technology may focus on intelligence, multi-function integration, and the deep integration of regenerative medicine and precision medicine. The exploration of intelligent biological dressings aims to realize real-time monitoring and treatment feedback of the wound environment by integrating Nanotechnology and biosensing and promote the precise release of personalized drugs or growth factors. The research and development of multifunctional biological dressings aims to integrate multiple therapeutic functions and comprehensively respond to the phased needs of wound healing. The combined application of regenerative medicine and 3D printing technology opens up a new path for the design of tissue engineering scaffolds, aiming to promote more natural tissue regeneration and precise repair. The precision medicine strategy based on omics data will further refine the individualized design of biological dressings, and the in-depth long-term effect and safety evaluation will provide a scientific cornerstone for the reliability and effectiveness of these emerging technologies.

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6. Conclusion

At present, biological dressing is an effective material for the treatment of diabetic-infected wounds. In recent years, more and more studies have shown that biological dressing technology shows great application potential in controlling infection, regulating the immune system, promoting tissue repair, and so on. These dressings can not only effectively inhibit the growth of a variety of pathogens, but also accelerate the wound closure process by regulating the local immune environment and accurately regulating the polarization state of immune cells, such as promoting the activation of M2 macrophages, fibroblast proliferation, angiogenesis and inflammatory balance, inhibiting excessive inflammatory response, reducing scar formation, and promoting tissue regeneration. In addition, the dynamic response ability of intelligent dressings, such as pH-responsive, glucose-responsive or ROS-responsive, shows the potential of accurately regulating the healing microenvironment, further promoting the development of diabetic wound treatment towards personalized and precision medicine. In the future, personalized biological dressings can be developed based on big data analysis such as genomics and proteomics to carry out precise treatment for each patient's specific situation.

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