Am J Transl Res 2021;13(12):13261-13272
www.ajtr.org /ISSN:1943-8141/AJTR0136759

Review Article

The role of gel wound dressings loaded with stem cells in the treatment of diabetic foot ulcers

Xionglin Chen[1], Jianfang Wu[2], Xiaoming Cao[3], He Jiang[1], Zhiren Wu[4], Zidu Zeng[4], Hui Chen[3], Jie Zhang[1]

Departments of [1]Histology & Embryology and Medical Genetics, [2]Pathogenic Biology and Immunology, [3]Anatomy, [4]Preventive Medicine, Grade 2019, School of Medicine, Jiujiang University, Jiujiang 332000, Jiangxi, China

Received June 25, 2021; Accepted November 3, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Diabetic foot ulcers (DFUs) are a serious complication of diabetes and the main cause of nontraumatic lower limb amputations, resulting in a serious economic burden on society. The main causes of DFUs include peripheral neuropathy, foot deformity, chronic inflammation, and peripheral artery disease. There are many clinical approaches for the treatment of DFUs, but they are all aimed at addressing a single aetiological factor. Stem cells (SCs), which express many cytokines and a variety of nerve growth factors and modulate immunological function in the wound, may accelerate DFU healing by promoting angiogenesis, cell proliferation, and nerve growth and regulating the inflammatory response. However, the survival time of SCs without scaffold support in the wound is short. Multifunctional gel wound dressings play a critical role in skin wound healing due to their ability to maintain SC survival for a long time, provide moisture and prevent electrolyte and water loss in DFUs. Among the many methods for clinical treatment of DFUs, the most successful one is therapy with gel dressings loaded with SCs. To accelerate DFU healing, gel wound dressings loaded with SCs are needed to promote the survival and migration of SCs and increase wound contraction. This review summarizes the research advancements regarding multifunctional gel wound dressings and SCs in the treatment of DFU to demonstrate the effectiveness and safety of this combinational therapeutic strategy.

Keywords: Diabetic foot ulcers, stem cell, wound dressing, gels

Introduction

Diabetes can lead to many complications, among which diabetic foot ulcers (DFUs) are one of the most serious. It is estimated that approximately 19-34% of diabetic patients develop DFUs in their lifetime. The International Diabetes Federation (IDF) has reported that approximately 91-26.1 million people develop DFUs every year [1, 2]. Poor DFU healing results in chronic wound development, which usually leads to amputation. DFUs are the main cause of nontraumatic lower limb amputations [3]. The main pathogenic factors of DFUs are chronic inflammation, peripheral artery disease and peripheral neuropathy. In addition, blood glucose may be poorly controlled for a long period in diabetic patients, and hyperglycaemia results in peripheral nerve fibre damage through a variety of mechanisms, including the activation of protein kinase C, the formation of advanced glycation end products, DNA damage and chronic inflammation [4].

Chronic inflammation plays a critical role in the pathogenesis of DFU. A variety of inflammatory cells have been observed to accumulate in the dermis and around the blood vessels of skin wounds in diabetic mice [5]. The characteristics of chronic inflammation in DFUs show an increase in the number of proinflammatory M1 macrophages and a decrease in the number of anti-inflammatory M2 macrophages. Studies have demonstrated that chronic inflammation is characterized by high expression levels of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [6]. In addition, oxygen supply plays a significant role in cell metabolism and energy production. Deficiencies in tissue perfusion and oxygen supply in DFUs due to microvascular and macrovascular lesions lead to hypoxia and delayed wound healing [7]. Moreover, peripheral vascular disease influences the blood flow of the lower extremities, which results in hypoxia in DFU healing. Some studies demonstrated that dia-

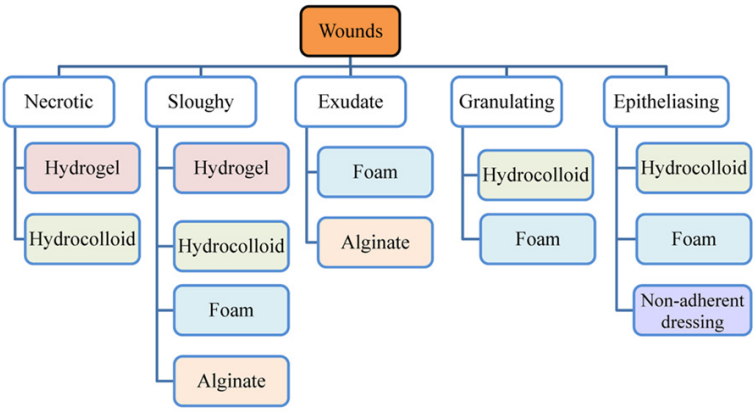

Figure 1. Classification of the different dressing types commonly used in DFU treatment [14].

betic neuropathy is closely related to microcirculation in DFUs [8, 9]. After skin trauma, peripheral nerve fibres are stimulated and produce a variety of neuropeptides around the skin wound. Neuropeptides are composed of P substances, neuropeptide Y and calcitonin gene-related peptides (CGRPs), which affect the functions of many cells, including mast cells, endothelial cells, fibroblasts, and keratinocytes, and accelerate angiogenesis, granulation tissue formation and re-epithelization in wound healing. These neuropeptides are critical regulatory factors in skin wound healing and can promote the proliferation of keratinocytes and dermal cells, promote nerve growth and maintain skin pain sensations, which are beneficial to DFU healing [10, 11].

Treatment strategies for DFUs include wound dressing, nonsurgical debridement, hyperbaric oxygen therapy, negative pressure wound therapy, human growth factor administration, skin transplantation and bioengineering approaches, stem cell (SC) therapy, vascular transplantation, blood glucose regulation and systemic therapy [12, 13]. Synthetic wound dressings include acrylic, membrane, foam, hydrocolloid, water fibrous and gel dressings. These wound dressings have been substituted for traditional dressings. The ideal wound dressing has the following characteristics: maintains wound cleanliness, provides a moist wound environment, prevents secondary infection, removes wound exudates, and promotes wound angiogenesis, granulation tissue regeneration and nerve growth. Choosing appropriate dressings for different types of wounds can promote wound healing (**Figure 1**) [14]. However, existing dressings cannot meet all the requirements of DFU treatment. The correct choice of dressing depends on the type of wound, the stage of wound development, the extent of injury, the condition of the patient and the tissue involved. Gels are complex hydrophilic organic cross-linking polymers composed of a water base of 80-90% [15]. These gels can conform freely to the shape of the wound to form amorphous or fixed flexible sheets. They can absorb the smallest amount of fluid by expansion, but they can also perform autolysis debridement on dry wounds and maintain a moist wound environment. Due to their high water content, gels can decrease wound temperature, accelerate granulation tissue formation and re-epithelialization, and alleviate pain. They allow the penetration of gas and water and can seal wounds and limit bacterial invasion [16].

However, ischemia, infection, peripheral neuropathy and glucose metabolism disorders often result in delayed DFU healing. Recent advances in research on the cellular and molecular complexities of wound healing indicate that coagulation, inflammation, cell migration, and proliferation are critical steps for tissue healing and remodelling. SCs can be derived from a wide range of sources, have the potential for self-renewal and differentiation, can synthesize various growth factors needed for wound healing and modulate immune function, which make SC therapy a new option for tissue repair and regeneration [17]. An increasing number of diseases can be ameliorated by SC therapy, including myocardial infarction, severe skin burns, Parkinson's disease, and DFUs [18].

In this review, we summarize the therapeutic effects and mechanisms of a variety of gel wound dressings and SCs and analyse the advantages of both dressings and SCs in the treatment of DFUs. We propose that therapy with gel wound dressings loaded with SCs is a promising treatment strategy for DFUs.

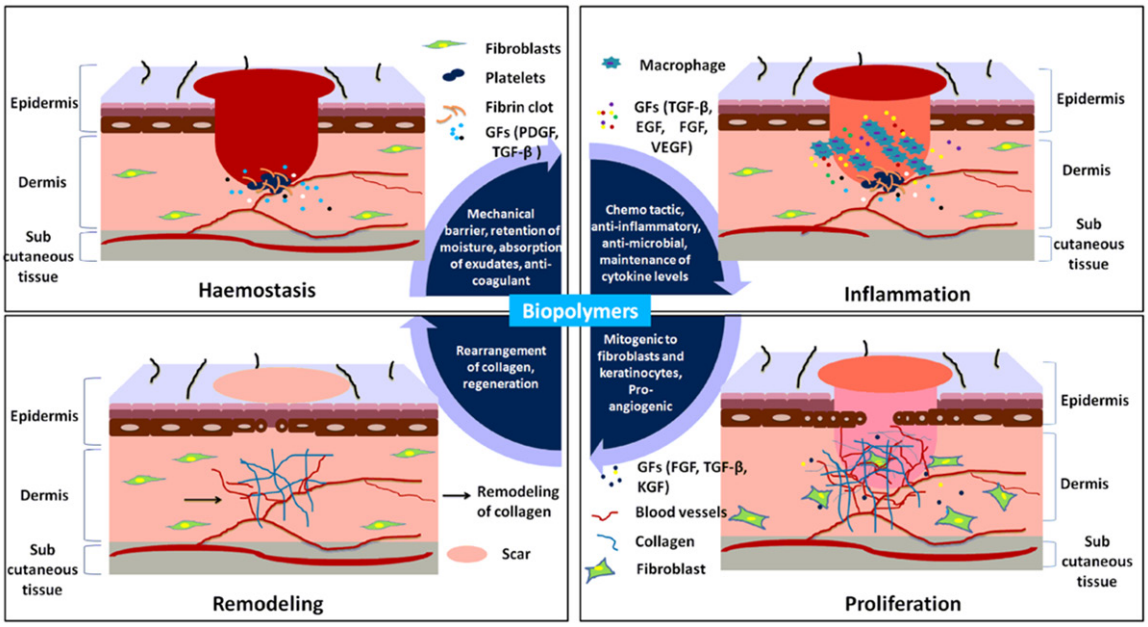

Figure 2. Phases of wound healing and the role of biopolymers during each phase of wound healing [19].

Application of stem cells in DFUs

Wound healing mainly comprises the following processes: haemostasis, inflammation, cell proliferation and wound remodelling. These processes involve a variety of cell types, many cytokines and extracellular matrix (**Figure 2**) [19]. The potential mechanism of DFU formation is unclear. The impaired healing of DFUs is related to hypoxia, vascular formation damage, reactive oxygen species damage, chronic inflammation and neuropathy [20]. However, some clinical treatments are ineffective for many patients due to cell damage, as cell functions around the wound are affected in DFUs [21]. To resolve this problem, SCs may be employed to recruit many cells, produce a variety of growth factors and synthesize additional proteins in the wound [22-25]. SCs have a unique differentiation ability that plays an important role in wound healing. SCs can mobilize to ischemic and injured tissues, where they secrete chemokines and growth factors and promote angiogenesis and the synthesis and remodelling of extracellular matrix. Therefore, SCs play an important role in wound healing [26]. However, SC therapy still has problems of immune rejection, limited differentiation and proliferation ability of SCs and chromosomal variation of SCs [27].

Many types of SCs are used in the treatment of skin wounds, such as bone marrow mesenchymal SCs (BMMSCs), umbilical cord mesenchymal SCs (UCMSCs), peripheral blood SCs (PBSCs), adipose-derived mesenchymal SCs (AMSCs), placenta-derived mesenchymal SCs (PMSCs), human amniotic fluid-derived stem cells (AFMSCs), and human gingival-derived mesenchymal SCs (GMSCs). Currently, BMMSCs are the most frequently used type [28]. BMMSCs have the potential to treat DFUs, and may be the best cell type for this purpose. Compared with other types of SCs, UCMSCs have many advantages, including a rich variety of sources, relative safety and short culture time in vitro. Many studies have shown that UCMSCs have similar characteristics, including fibroblast morphology, typical immunophenotype markers and multiple differentiation potential [29]. In addition, UCMSCs have low immunogenicity [30, 31]. Studies of the use of AMSCs, PMSCs and AFMSCs in DFU healing have been performed, but no clinical trials have been reported. Human gingival-derived mesenchymal SCs (GMSCs) were studied in a model of cut-off wounds, but the data were very limited. Recent research has demonstrated that human induced pluripotent SC-derived smooth muscle cells (hiPSC-SMCs) also have the potential to accelerate wound healing in diabetes [32].

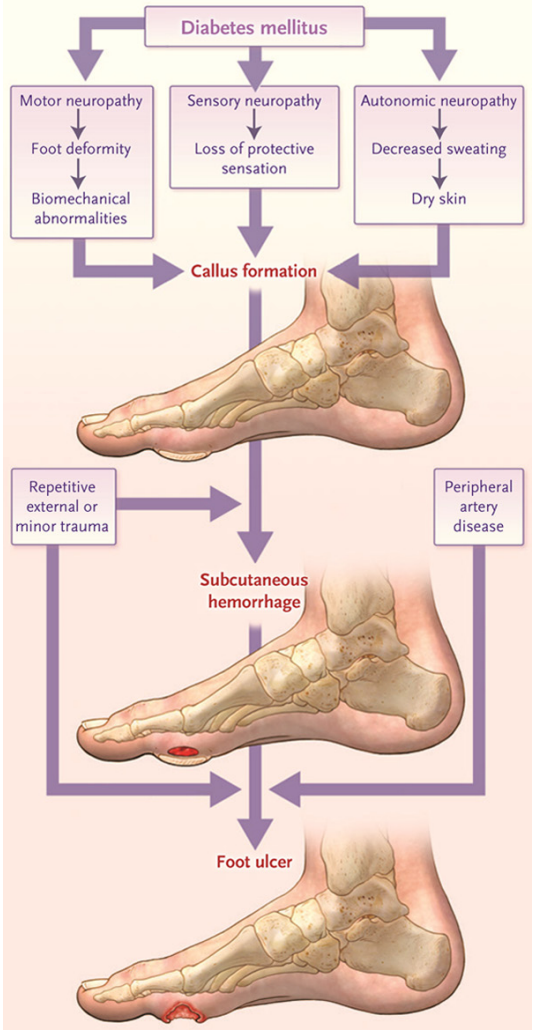

Figure 3. Diabetic foot ulcers and their recurrences are caused by a number of factors that ultimately lead to skin breakdown. These factors include sequelae related to sensory, autonomic, and motor neuropathies [33].

The wound surface of DFUs is characterized by chronic trauma, exhibiting peripheral neuropathy, poor collagen synthesis, chronic inflammation, decreased growth factors, vascular formation disorder and difficulty in epidermal regeneration. Peripheral neuropathy results in lesions of sensory, motor, and autonomic nerves and impaired function in the lower extremities (**Figure 3**) [33]. However, there are many pathogenic factors related to peripheral neuropathy, including hyperglycaemia, nonenzymatic glycation, oxidative stress, ischemic hypoxic factors, abnormal nerve growth factors, polyol pathway activation, and immune abnormalities [34]. These factors can lead to microvascular disease of the lower extremities, which aggravates ulcers. Thus, therapy for diabetic peripheral neuropathy may prevent or contribute to the recovery of DFUs, which decreases the risk of lower limb amputation. Research has shown that denervation causes difficulty in wound enlargement and re-epithelization and decreases the axon density of the epidermis and dermis, resulting in delayed wound healing [35].

Studies have shown that the density of skin fibres and the level of neuropeptides decrease after peripheral nerve transection, where the skin loses its innervation, which leads to a decrease in cell proliferation around the wound and wound healing delay. BMSCs synthesize a variety of antioxidant, neuroprotective, angiogenic and immunomodulatory factors, which are decreased in the peripheral nerves of DFUs [28]. In addition, increases in these factors can be improved by incubating BMSCs under pretreatment stimulation in vitro, thus enhancing their therapeutic effect on wounds. Studies have shown that BMSCs can express these factors after pretreatment in vitro. In these studies, BMSCs expressing these factors were transplanted into DFUs. Wound-protective factors promoted the healing of multiple neuropathies and prevented the formation of DFUs. Moreover, these factors significantly restored the efficacy of diabetic polyneuropathy, increased the density of epidermal nerve fibres, reduced the apoptosis of neurons and Schwann cells, promoted angiogenesis, and reduced chronic wound inflammation [36].

Types of gel wound dressings and their application in wound healing

Traditional dressings mainly include bandages, sterile gauze, and cotton pads. Moisturizing dressings include membranes, gels, hydrocolloids, foams and water fibres. Dressings impregnated with antimicrobial agents can be used for wounds with surface infection or at high risk of infection. In recent years, gels have been extensively studied as wound dressings. Gels can maintain the moisture of the wound and promote wound angiogenesis and cell proliferation. They have been proven to be beneficial for skin tissue engineering [37].

Gels comprise a single or mixed hydrated polymer, showing gelation. Covalent or noncovalent

cross-linking can be used to control their expansion capacity and maintain their conformational structure, features conducive to maintaining a moist environment surrounding the wound. In addition, gels may reversibly expand or contract in an aqueous environment at a specific pH and ionic strength. Gel wound dressings are suitable for dry wounds but not for exudative wounds. These wound dressings have flexibility and no antigenicity and are conducive to the infiltration of water, oxygen and metabolites. They usually interfere with the removal of wounds [38]. Polymers consist of synthetic or semisynthetic methacrylate polymers, methyl cellulose, propylene glycol, pectin, collagen, alginate, and chitosan. The insoluble methylacrylate polymer has a certain tension, and it forms a three-dimensional network by combining with synthetic or semisynthetic hydrophilic water [39]. Necrotic tissue and pathogenic microorganisms can be incorporated into gel dressings, and ulcers can be healed. The gels may maintain a moist environment on the wound surface, which stimulates new granulation tissue growth and epithelial cell migration. Because the gels of wound dressings have high water content, they can reduce pain by cooling wounds [40].

Alginate is one of the most critical polysaccharides employed in tissue engineering and drug release research. Alginate is abundant in nature and is mainly found in marine brown algae, sarcophagus, polycystis and some soil bacteria pod polysaccharides. It consists of b-d-mannuronic acid and a-l-gulolacturonic acid residues. Alginate can interact with divalent cations (such as Ca^{2+}, Mg^{2+}, Ba^{2+} and Mn^{2+}) to form a reversible gel, which can be cross-linked with G-residues of the sodium alginate chain through ionic interactions [41]. Alginate can be used as a three-dimensional scaffold for cell transplantation and in biomaterial wound dressings because of its simple cross-linking and processing. In addition, alginate has good biocompatibility, low toxicity and good adhesion. However, alginate gels may undergo uncontrolled degradation and dissolution after the loss of divalent cationic cross-linkers. To resolve this problem, covalent/ionic cross-linking can be employed as a substitute for other biopolymers, such as gelatine, heparin, polyvinyl alcohol, and chitosan. Another major disadvantage of alginate biomaterials is that they can not be effectively and rapidly degraded in mammalian wounds. Calcium alginate gel wound dressings are effective in absorbing exudates from wounds. Therefore, these types of dressings are beneficial for DFU debridement and healing [42, 43].

Gelatine is derived from collagen derivatives. It has low antigenicity and good biocompatibility and is simple to synthesize. In medicine and biomedical applications, it is usually used as a gel scaffold. Gelatine can be obtained by the denaturation of collagen under acidic or alkaline conditions [44]. Therefore, according to the different collagen pretreatment methods, two different types of gelatine can be obtained. The pretreatment of gelatine under acidic or alkaline conditions affects the isoelectric point of biomaterials. Various manufacturers synthesize gelatine biomaterials with different isoelectric points according to pH values from acidic to alkaline. This variation in the isoelectric point value is important because it affects the combination of gelatine with positively or negatively charged biological molecules. Alkaline gelatine is the best carrier for acid bioactive molecules, and it can be used to release alkaline bioactive substances [45].

In recent years, fibrin biomaterials (such as modified/cross-linked fibrin and fibrin complexes) have attracted much attention as drug and cell scaffolds in tissue engineering applications. Fibrin gels can enhance wound angiogenesis and neurite outgrowth [46]. A major drawback of fibrin gels is that they have low mechanical hardness and may degrade quickly in wounds. Fibrin gels are composed of a combination of fibrinogen and thrombin and are formed through enzymatic hydrolysis. Thus, the final structural state of fibrin gels is dependent on many factors, such as thrombin and fibrinogen concentrations, local pH, ionic strength, and local calcium concentration. Studies have shown that the use of fibrin gels loaded with haematopoietic SCs can promote wound healing. Pluripotent SCs can differentiate into fibroblasts, keratinocytes and endothelial cells, which may play important roles in wound healing [47].

Polyethylene glycol can be mixed with other polymers, such as chitosan and lactic-co-glycolic acid copolymer propylene fumarate, to adjust its inherent solubility, corrosiveness,

mechanical and thermal properties, crystallinity and viscosity. Gels composed of polyethylene glycol composite biomaterials have been widely utilized in many biomedical fields, such as wound dressings and drug carriers [48]. These gels promote skin cell proliferation, enhance collagen deposition and reduce scar formation, and they have been shown to accelerate DFU healing. Polyethylene glycol can be combined with other polymers, such as polycaprolactone, and can be loaded with growth factors, such as epidermal growth factor (EGF) and basic fibroblast growth factor (bEGF), to accelerate skin wound healing by promoting angiogenesis, collagen synthesis and re-epithelization [49].

Polyvinylpyrrolidone gels have good hydrophilicity and biocompatibility. As biomaterials, they have been widely favoured in wound dressings. They also have water absorption ability and oxygen permeability. Polyvinylpyrrolidone gels are inexpensive to produce, and their synthesis process is simple, safe and efficient. Polyvinylpyrrolidone can be mixed with other polymers (such as agar, cellulose or polyethylene glycol) or cross-linked with carbodiimide [50]. The solubility, erosive properties, mechanical properties, softness, and elasticity of polyvinylpyrrolidone can be modulated by cross-linking with these other polymers. Studies have shown that when S-glutathione, an endogenous glutathione, or its oligomeric derivative chelating agent is grafted onto vinyl methyl ether maleic anhydride, a complex is formed with polyvinyl pyrrolidone complex gels, which can release nitric oxide on the wound surface. Compound gels of wound dressings can release NO continuously, and the local release of NO can accelerate wound healing [51].

Poly (hydroxyethyl methacrylate) (pHEMA) has good biocompatibility and nondegradability. This polymer can form gels for use as wound dressings to promote wound healing. The final physicochemical properties, adsorption and permeability of the polymer depend on the synthesis method and conditions, the chemical properties of the comonomer and the cross-linking agent, and the final cross-linking degree. Polymer gels composed of pHEMA usually have good oxygen permeability, water absorption, and biocompatibility and are nontoxic. pHEMA gels have been used in wound dressings, and many bioactive substances can be incorporated into these materials [48].

Application of gel scaffolds loaded with SCs in DFU therapy

Combination therapy of biomaterials and SCs has attracted extensive attention in the treatment of DFUs. These advanced biomaterials can maintain cell viability and promote SC proliferation and differentiation. The theory of wound wetness has attracted the attention of scholars. A moist wound environment is instrumental for cell proliferation and angiogenesis [52], and new tissue engineering strategies have been introduced in the treatment of DFUs. Combination therapy with SCs and composite biomaterials will be helpful to determine the characteristics of SCs and biomaterial scaffolds that are conducive to DFU healing. The use of multifunctional wound dressings combined with SC therapy represents a major breakthrough.

The chronic inflammatory response in DFUs involves a variety of cytokines [14], including proinflammatory and anti-inflammatory cytokines. Proinflammatory factors result in the aggravation of inflammation. Anti-inflammatory factors can suppress the synthesis of proinflammatory factors, influence the antigen presentation ability of monocytes, inhibit the function of T and B cells, and maintain the balance of the cytokine network in the body [53]. Therefore, treatment strategies that regulate the inflammatory response can promote skin wound healing. Combination biomaterial gels composed of dermal matrix, MSCs, and timolol have been shown to accelerate DFU healing in mice by modulating the production of inflammatory factors. Furthermore, studies have demonstrated that in the early inflammatory stage of the wound healing process, a compound gel loaded with BMSCs can decrease the levels of proinflammatory cytokines including IL-1β and IL-6, inhibit granulocyte infiltration, and change the ratio of M2/M1 macrophages. Importantly, the proliferation of vascular endothelial cells has been observed with this treatment. In general, combination gels have successfully increased wound healing and reduced the wound inflammatory reaction in diabetic patients with chronic wounds [54].

Viezzer et al. synthesized a new chitosan-polyurethane gel membrane. The gel membrane had low cytotoxicity and promoted wound healing when it was used in conjunction with BMSCs in diabetic rats. Biodegradable gels were pro-

duced in block copolymer networks and, combined with chitosan blocks and biodegradable polyurethanes. Research has demonstrated that this type of gel membrane has interesting properties that make it suitable for promoting DFU healing [55]. In an animal experiment, AMSCs were preincubated in a hyaluronic acid sponge gel in neurogenic/standard medium and then transplanted into full-thickness wounds of diabetic mice. Acellular sponge gels were used in the control group. Four weeks after transplantation, a thicker and more differentiated epidermis was observed in the group treated with cellular sponge gels. Two weeks post-trauma, an accelerated progression from the inflammatory stage to the proliferation stage was observed during wound healing in the experimental groups. However, the M2/M1 ratio was significantly increased in the neurogenic preconditioning group, but it did not accelerate the growth of new nerves. The results of that study suggest that the use of sponge-like gels loaded with SCs is a promising way to enhance the healing of DFUs by actively influencing the occurrence of re-epithelialization and regulating the inflammatory response to promote neural innervation [56].

Hao et al. synthesized a new type of self-healing gel through the in situ cross-linking of N-carboxyethyl chitosan (N-chitosan) and adipic acid dihydrazide (ADH) with hyaluronic acid aldehyde (HA-ALD), and the gels had hydrating and antimicrobial properties. The combination of biomaterials containing gels and SCs can promote the proliferation of SCs and the secretion of growth factors, which accelerates wound healing. The results showed that the injectable and self-repairing gels had good swelling properties, stability and mechanical properties. This biocompatible gel can regulate skin wound inflammation and promote granulation tissue formation, collagen deposition, nuclear cell proliferation, and neovascularization by stimulating bone marrow stromal cells to secrete a variety of growth factors and regulating the secretion of proinflammatory and anti-inflammatory factors [57].

A clinical experiment was conducted wherein hyaluronic acid gels loaded with UCMSCs and umbilical cord blood-derived endothelial colony forming cells (ECFCs) were injected into skin wounds. The results demonstrated that after 4 weeks of therapy, the skin wounds of 6 patients healed completely, and the wounds of the remaining 6 patients were significantly reduced. The study shows that the combination of UCMSCs, ECFCs and gels can safely accelerate the healing of refractory DFUs [58]. In addition, the effect of collagen as a dressing combined with SCs in the treatment of DFUs has been reported. Collagen gel scaffolds containing hiPSC-SMCs can promote DFU healing, and the mechanism of healing involves the increased production of anti-inflammatory factors by M2 macrophages [32]. In addition, degradable collagen gels combined with autologous skin fibroblasts and MSCs have been applied to treat DFUs. Over 29 days of treatment, the wound surface gradually diminished, and the thickness of dermal vessels increased. These findings demonstrated that the application of combination therapy can increase the healing of DFUs [59].

A study demonstrated that collagen gels loaded with MSCs derived from non-diabetic bone marrow promoted the DFU healing by increasing angiogenesis. Acceleration of wound healing as evaluated based on the percentage of wound contraction was observed only when large numbers of cells were used [60]. Another study showed that a combination of treatment involving SC exposure to osteopontin and SC implantation in collagen dressing gels both promoted DFU healing and reduced the DFU area. Collagen gels and collagen gels loaded with SCs can increase angiogenesis in DFUs [61].

Nilforoushzadeh et al. reported a case of type 2 diabetes with DFU-related osteomyelitis. The combination of chloroacetic acid, calcium alginate and foam dressing and the injection of human fibroblasts and fibroblast seeding collagen gels had a positive effect on DFUs. After six months of therapy, the wound area was greatly reduced, and collagen fibre proliferation was observed. These results suggest that this combination therapy is very effective in the treatment of DFU-associated osteomyelitis and can prevent amputation in DFU patients [62]. Peptide-based FHE gels (F127/OHA-EPL), which have antibacterial functions, synergize with AMSCs to accelerate skin wound healing by accelerating the healing of chronic wounds and facilitating entire skin regeneration in DFU patients [63]. In addition, bioactive materials

such as curcumin, aloe and hyaluronic acid have great potential in the treatment of DFU when combined with SCs as gel dressings [64]. With further research, gel wound dressings loaded with SCs will provide more treatment options for patients with DFU.

Damage to the blood supply caused by vascular disease is an important pathological factor of nonhealing DFUs. Local application of allogeneic BMSCs can increase angiogenesis to promote skin wound healing. Direct injection of BMMSCs into DFUs has been shown to result in a short cell survival time. Synthesized biomaterials composed of collagen gels loaded with BMSCs can support cell survival and improve the therapeutic effect. These synthesized biomaterials can deliver BMSCs to DFUs and accelerate DFU healing. The potential mechanisms of wound healing include increasing the paracrine activity of growth factors and chemokines required for wound healing, promoting the differentiation of keratinocytes and increasing the endothelial cell proliferation required for angiogenesis [65]. BMSCs can be carried by gel biomaterials and have the functions of immunosuppression and immunoregulation. Stem cell therapy can improve the rate of wound healing, promote new granulation tissue formation, promote angiogenesis, and increase the number of cells associated with wound healing. The combination of biomaterials and SC therapy in vivo can maintain the viability and function of cells [55]. Biomaterials such as collagen gel can target a large number of SCs in the wound. It has been speculated that in an animal model of diabetic skin ulcers, the local application of collagen scaffolds inoculated with allogeneic BMSCs can promote wound angiogenesis and increase skin wound healing [60].

In addition, a study demonstrated that gellan gum hyaluronic acid (GG-HA) sponge gels loaded with microvascular endothelial cells and human adipose tissue-derived SCs (HASCs) accelerated DFU healing [66]. Functional wound dressings with specific physical, chemical and biological characteristics are very important for the treatment of DFUs [18, 67]. Accordingly, collagen, chitosan and alginate have been widely studied. Among the various types of dressings, collagen gel dressings can promote the migration, proliferation and differentiation of a variety of cells associated with wound healing and the secretion of growth factors [68]. Chitosan is a type of natural high polymer polysaccharide that is the only basic polysaccharide currently used in gel dressings. It is a bioactive polymer with antibacterial and other functional properties and is nontoxic, biodegradable and widely used [69]. Alginate is a linear polysaccharide mainly produced by brown algae in the marine environment. Alginate is composed of a linear block copolymer comprising two monomer units. It is mainly used in drug release and plays a role in hemostasis and wound healing [70]. Studies of combination dressings are also being conducted. A study reported the feasibility of acetate/gelatine (CA/gel) electrospinning pads with berberine (beri) as a special wound dressing for DFU [71]. How to combine these dressings with SCs is also a problem worthy of consideration in future research. In addition, the new wound dressings also include some nanomaterials. The results of several studies suggest broad prospects for the application of these materials in the treatment of DFUs [72, 73]. These studies also provide a theoretical basis for the use of wound dressings and SCs in the treatment of DFUs.

Summary and future prospects

DFUs are a major cause of nontraumatic lower limb amputation. The pathophysiological study of DFUs has shown that DFUs can be caused by multiple factors. The process of DFU healing is complex, and improved understanding of the related mechanisms will facilitate the development of targeted treatment for DFUs. Clinical treatment methods for DFUs mainly include the regulation of blood glucose and the nourishment of peripheral nerves, skin flap transplantation, wound debridement, arterial interventional therapy, dressing use, cytokine application, SC transplantation, hyperbaric oxygen therapy, antibiotic therapy and gene therapy [28, 74, 75]. In recent years, exosomes that can promote wound healing by transferring their mRNA, miRNA and protein to target cells have attracted extensive attention. Exosomes secreting specific antibiotics, cytokines, and nerve growth factors can promote DFU healing through a variety of pathways [76]. However, the most commonly used method of exosome administration is injection, which affects exosome function. Furthermore, DFU healing

requires a long time. Therefore, it is necessary to develop new wound dressings loaded with exosomes to maintain their bioactivity and accelerate DFU healing.

However, some DFUs are highly resistant to common treatment methods. SC-based therapies, gene therapy and neuropeptide administration are emerging treatments for chronic wounds that are refractory to standard therapies. SCs that express specific cytokines and nerve growth factors by gene recombination technology, which accelerate DFU healing via multiple mechanisms, will be a future direction in the development of DFU therapies. The use of advanced biomaterials to maintain SC survival, proliferation and differentiation in combination therapy has attracted extensive attention. In this review, we provide an overview of the background and theoretical basis of SC-loaded wound dressing therapy as well as the latest research progress. The evidence provided supports the view that the clinical use of combination therapy comprising SCs and gel wound dressings will benefit DFU patients.

Acknowledgements

This work was supported by the Natural Science Foundation of China (81960159), Jiangxi Provincial Natural Science Foundation (20202BAB206022), Science and Technology Research Foundation of Educational Department of Jiangxi Province (GJJ190004), and Science and Technology Program Foundation of Health and Family Planning Commission of Jiangxi Province (20193009).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xionglin Chen, Department of Histology & Embryology and Medical Genetics, School of Medicine, Jiujiang University, 551 East Qianjin Road, Jiujiang 332000, Jiangxi, China. Tel: +86-0792-8570078; Fax: +86-0792-8570078; E-mail: cxl97@126.com

References

[1] Cao L, G Adedjouma N, Xu C, Shen KW, Laki F, Chen JY and Kirova YM. The role of post-mastectomy radiotherapy in elderly patients with 1-3 positive lymph nodes breast cancer: an international retrospective double-center study. Breast J 2019; 25: 107-111.

[2] Park KH, Kwon JB, Park JH, Shin JC, Han SH and Lee JW. Collagen dressing in the treatment of diabetic foot ulcer: a prospective, randomized, placebo-controlled, single-center study. Diabetes Res Clin Pract 2019; 156: 107861.

[3] Mulder GD, Patt LM, Sanders L, Rosenstock J, Altman MI, Hanley ME and Duncan GW. Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. Wound Repair Regen 1994; 2: 259-269.

[4] Rekha PD, Rao SS, Sahana TG and Prabhu A. Diabetic wound management. Br J Community Nurs 2018; 23 Suppl 9: S16-S22.

[5] Serban D, Papanas N, Dascalu AM, Stana D, Nicolae VA, Vancea G, Badiu CD, Tanasescu D, Tudor C, Balasescu SA and Pantea-Stoian A. Diabetic retinopathy in patients with diabetic foot ulcer: a systematic review. Int J Low Extrem Wounds 2021; 20: 98-103.

[6] Suzuki T, Gao J, Ishigaki Y, Kondo K, Sawada S, Izumi T, Uno K, Kaneko K, Tsukita S, Takahashi K, Asao A, Ishii N, Imai J, Yamada T, Oyadomari S and Katagiri H. ER stress protein CHOP mediates insulin resistance by modulating adipose tissue macrophage polarity. Cell Rep 2017; 18: 2045-2057.

[7] Baltzis D, Eleftheriadou I and Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. Adv Ther 2014; 31: 817-836.

[8] Lopez-Moral M, Lazaro-Martinez JL, Garcia-Morales E, Garcia-Alvarez Y, Alvaro-Afonso FJ and Molines-Barroso RJ. Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polineuropathy: a randomized clinical trial. PLoS One 2019; 14: e0219537.

[9] Dinh T, Tecilazich F, Kafanas A, Doupis J, Gnardellis C, Leal E, Tellechea A, Pradhan L, Lyons TE, Giurini JM and Veves A. Mechanisms involved in the development and healing of diabetic foot ulceration. Diabetes 2012; 61: 2937-2947.

[10] Kant V, Kumar D, Prasad R, Gopal A, Pathak NN, Kumar P and Tandan SK. Combined effect of substance P and curcumin on cutaneous wound healing in diabetic rats. J Surg Res 2017; 212: 130-145.

[11] Kim S, Piao J, Hwang DY, Park JS, Son Y and Hong HS. Substance P accelerates wound repair by promoting neovascularization and preventing inflammation in an ischemia mouse model. Life Sci 2019; 225: 98-106.

[12] Everett E and Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci 2018; 1411: 153-165.
[13] Blume P and Wu S. Updating the diabetic foot treatment algorithm: recommendations on treatment using advanced medicine and therapies. Wounds 2018; 30: 29-35.
[14] Moura LI, Dias AM, Carvalho E and de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment--a review. Acta Biomater 2013; 9: 7093-7114.
[15] Saldin LT, Cramer MC, Velankar SS, White LJ and Badylak SF. Extracellular matrix hydrogels from decellularized tissues: structure and function. Acta Biomater 2017; 49: 1-15.
[16] Alven S and Aderibigbe BA. Chitosan and cellulose-based hydrogels for wound management. Int J Mol Sci 2020; 21: 9656.
[17] Su L, Zheng J, Wang Y, Zhang W and Hu D. Emerging progress on the mechanism and technology in wound repair. Biomed Pharmacother 2019; 117: 109191.
[18] Cao Y, Gang X, Sun C and Wang G. Mesenchymal stem cells improve healing of diabetic foot ulcer. J Diabetes Res 2017; 2017: 9328347.
[19] Sahana TG and Rekha PD. Biopolymers: applications in wound healing and skin tissue engineering. Mol Biol Rep 2018; 45: 2857-2867.
[20] Guo S and Dipietro LA. Factors affecting wound healing. J Dent Res 2010; 89: 219-229.
[21] Pop MA and Almquist BD. Biomaterials: a potential pathway to healing chronic wounds? Exp Dermatol 2017; 26: 760-763.
[22] Golchin A, Farahany TZ, Khojasteh A, Soleimanifar F and Ardeshirylajimi A. The clinical trials of mesenchymal stem cell therapy in skin diseases: an update and concise review. Curr Stem Cell Res Ther 2019; 14: 22-33.
[23] Squillaro T, Peluso G and Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell Transplant 2016; 25: 829-848.
[24] Oskarsson B, Gendron TF and Staff NP. Amyotrophic lateral sclerosis: an update for 2018. Mayo Clin Proc 2018; 93: 1617-1628.
[25] Li B, Luan S, Chen J, Zhou Y, Wang T, Li Z, Fu Y, Zhai A and Bi C. The MSC-derived exosomal lncRNA H19 promotes wound healing in diabetic foot ulcers by upregulating PTEN via MicroRNA-152-3p. Mol Ther Nucleic Acids 2020; 19: 814-826.
[26] Frykberg RG and Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care (New Rochelle) 2015; 4: 560-582.
[27] Volarevic V, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N, Armstrong L, Djonov V, Lako M and Stojkovic M. Ethical and safety issues of stem cell-based therapy. Int J Med Sci 2018; 15: 36-45.
[28] Lopes L, Setia O, Aurshina A, Liu S, Hu H, Isaji T, Liu H, Wang T, Ono S, Guo X, Yatsula B, Guo J, Gu Y, Navarro T and Dardik A. Stem cell therapy for diabetic foot ulcers: a review of preclinical and clinical research. Stem Cell Res Ther 2018; 9: 188.
[29] Mahmood R, Choudhery MS, Mehmood A, Khan SN and Riazuddin S. In vitro differentiation potential of human placenta derived cells into skin cells. Stem Cells Int 2015; 2015: 841062.
[30] Zhang S, Chen L, Zhang G and Zhang B. Umbilical cord-matrix stem cells induce the functional restoration of vascular endothelial cells and enhance skin wound healing in diabetic mice via the polarized macrophages. Stem Cell Res Ther 2020; 11: 39.
[31] Baksh D, Yao R and Tuan RS. Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells 2007; 25: 1384-1392.
[32] Gorecka J, Gao X, Fereydooni A, Dash BC, Luo J, Lee SR, Taniguchi R, Hsia HC, Qyang Y and Dardik A. Induced pluripotent stem cell-derived smooth muscle cells increase angiogenesis and accelerate diabetic wound healing. Regen Med 2020; 15: 1277-1293.
[33] Armstrong DG, Boulton AJM and Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376: 2367-2375.
[34] Razzaghi R, Pidar F, Momen-Heravi M, Bahmani F, Akbari H and Asemi Z. Magnesium supplementation and the effects on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. Biol Trace Elem Res 2018; 181: 207-215.
[35] O'Brien TD. Impaired dermal microvascular reactivity and implications for diabetic wound formation and healing: an evidence review. J Wound Care 2020; 29 Suppl 9: S21-S28.
[36] Qi L, Ahmadi AR, Huang J, Chen M, Pan B, Kuwabara H, Iwasaki K, Wang W, Wesson R, Cameron AM, Cui S, Burdick J and Sun Z. Major improvement in wound healing through pharmacologic mobilization of stem cells in severely diabetic rats. Diabetes 2020; 69: 699-712.
[37] da Silva LP, Cerqueira MT, Sousa RA, Reis RL, Correlo VM and Marques AP. Engineering cell-adhesive gellan gum spongy-like hydrogels for regenerative medicine purposes. Acta Biomater 2014; 10: 4787-4797.
[38] Klotz BJ, Gawlitta D, Rosenberg AJWP, Malda J and Melchels FPW. Gelatin-methacryloyl hydrogels: towards biofabrication-based tissue repair. Trends Biotechnol 2016; 34: 394-407.
[39] Chaudhari AA, Vig K, Baganizi DR, Sahu R, Dixit S, Dennis V, Singh SR and Pillai SR. Fu-

ture prospects for scaffolding methods and biomaterials in skin tissue engineering: a review. Int J Mol Sci 2016; 17: 1974.
[40] Hsu KC, Luan CW and Tsai YW. Review of silicone gel sheeting and silicone gel for the prevention of hypertrophic scars and keloids. Wounds 2017; 29: 154-158.
[41] Zhang M and Zhao X. Alginate hydrogel dressings for advanced wound management. Int J Biol Macromol 2020; 162: 1414-1428.
[42] Zhang X, Sun D and Jiang GC. Comparative efficacy of nine different dressings in healing diabetic foot ulcer: a Bayesian network analysis. J Diabetes 2019; 11: 418-426.
[43] Geanaliu-Nicolae RE and Andronescu E. Blended natural support materials-collagen based hydrogels used in biomedicine. Materials (Basel) 2020; 13: 5641.
[44] Hussain Z, Thu HE, Shuid AN, Katas H and Hussain F. Recent advances in polymer-based wound dressings for the treatment of diabetic foot ulcer: an overview of state-of-the-art. Curr Drug Targets 2018; 19: 527-550.
[45] Gaspar-Pintiliescu A, Stanciuc AM and Craciunescu O. Natural composite dressings based on collagen, gelatin and plant bioactive compounds for wound healing: a review. Int J Biol Macromol 2019; 138: 854-865.
[46] Heher P, Muhleder S, Mittermayr R, Redl H and Slezak P. Fibrin-based delivery strategies for acute and chronic wound healing. Adv Drug Deliv Rev 2018; 129: 134-147.
[47] Whelan D, Caplice NM and Clover AJ. Fibrin as a delivery system in wound healing tissue engineering applications. J Control Release 2014; 196: 1-8.
[48] Razavi M, Qiao Y and Thakor AS. Three-dimensional cryogels for biomedical applications. J Biomed Mater Res A 2019; 107: 2736-2755.
[49] Garcia Garcia C and Kiick KL. Methods for producing microstructured hydrogels for targeted applications in biology. Acta Biomater 2019; 84: 34-48.
[50] Westby MJ, Dumville JC, Soares MO, Stubbs N and Norman G. Dressings and topical agents for treating pressure ulcers. Cochrane Database Syst Rev 2017; 6: CD011947.
[51] Buchsel PC. Polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair): a bioadherent oral gel for the treatment of oral mucositis and other painful oral lesions. Expert Opin Drug Metab Toxicol 2008; 4: 1449-1454.
[52] Nour S, Baheiraei N, Imani R, Khodaei M, Alizadeh A, Rabiee N and Moazzeni SM. A review of accelerated wound healing approaches: biomaterial-assisted tissue remodeling. J Mater Sci Mater Med 2019; 30: 120.
[53] Munkholm K, Brauner JV, Kessing LV and Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res 2013; 47: 1119-1133.
[54] Yang HY, Fierro F, So M, Yoon DJ, Nguyen AV, Gallegos A, Bagood MD, Rojo-Castro T, Alex A, Stewart H, Chigbrow M, Dasu MR, Peavy TR, Soulika AM, Nolta JA and Isseroff RR. Combination product of dermal matrix, human mesenchymal stem cells, and timolol promotes diabetic wound healing in mice. Stem Cells Transl Med 2020; 9: 1353-1364.
[55] Viezzer C, Mazzuca R, Machado DC, de Camargo Forte MM and Gomez Ribelles JL. A new waterborne chitosan-based polyurethane hydrogel as a vehicle to transplant bone marrow mesenchymal cells improved wound healing of ulcers in a diabetic rat model. Carbohydr Polym 2020; 231: 115734.
[56] da Silva LP, Santos TC, Rodrigues DB, Pirraco RP, Cerqueira MT, Reis RL, Correlo VM and Marques AP. Stem cell-containing hyaluronic acid-based spongy hydrogels for integrated diabetic wound healing. J Invest Dermatol 2017; 137: 1541-1551.
[57] Bai H, Kyu-Cheol N, Wang Z, Cui Y, Liu H, Liu H, Feng Y, Zhao Y, Lin Q and Li Z. Regulation of inflammatory microenvironment using a self-healing hydrogel loaded with BM-MSCs for advanced wound healing in rat diabetic foot ulcers. J Tissue Eng 2020; 11: 204173142-0947242.
[58] Zhao L, Guo Z, Chen K, Yang W, Wan X, Zeng P, He H, Luo Y, Xiao Q and Mo Z. Combined transplantation of mesenchymal stem cells and endothelial colony-forming cells accelerates refractory diabetic foot ulcer healing. Stem Cells Int 2020; 2020: 8863649.
[59] Vojtassak J, Danisovic L, Kubes M, Bakos D, Jarabek L, Ulicna M and Blasko M. Autologous biograft and mesenchymal stem cells in treatment of the diabetic foot. Neuro Endocrinol Lett 2006; 27 Suppl 2: 134-137.
[60] O'Loughlin A, Kulkarni M, Creane M, Vaughan EE, Mooney E, Shaw G, Murphy M, Dockery P, Pandit A and O'Brien T. Topical administration of allogeneic mesenchymal stromal cells seeded in a collagen scaffold augments wound healing and increases angiogenesis in the diabetic rabbit ulcer. Diabetes 2013; 62: 2588-2594.
[61] O'Loughlin A, Kulkarni M, Vaughan EE, Creane M, Liew A, Dockery P, Pandit A and O'Brien T. Autologous circulating angiogenic cells treated with osteopontin and delivered via a collagen scaffold enhance wound healing in the alloxan-induced diabetic rabbit ear ulcer model. Stem Cell Res Ther 2013; 4: 158.
[62] Nilforoushzadeh MA, Heidari-Kharaji M, Zare M, Zare S, Baiat Tork B and Jaffary F. Combina-

tion therapy of trichloroacetic acid, human autologous fibroblast injection and fibroblast seeded microfibrous collagen scaffold as a novel treatment for osteomyelitis diabetic foot ulcer. J Diabetes Investig 2021; 12: 1112-1117.

[63] Wang C, Wang M, Xu T, Zhang X, Lin C, Gao W, Xu H, Lei B and Mao C. Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration. Theranostics 2019; 9: 65-76.

[64] Shao M, Hussain Z, Thu HE, Khan S, de Matas M, Silkstone V, Qin HL and Bukhari SNA. Emerging trends in therapeutic algorithm of chronic wound healers: recent advances in drug delivery systems, concepts-to-clinical application and future prospects. Crit Rev Ther Drug Carrier Syst 2017; 34: 387-452.

[65] Kaisang L, Siyu W, Lijun F, Daoyan P, Xian CJ and Jie S. Adipose-derived stem cells seeded in Pluronic F-127 hydrogel promotes diabetic wound healing. J Surg Res 2017; 217: 63-74.

[66] Cerqueira MT, da Silva LP, Santos TC, Pirraco RP, Correlo VM, Reis RL and Marques AP. Gellan gum-hyaluronic acid spongy-like hydrogels and cells from adipose tissue synergize promoting neoskin vascularization. ACS Appl Mater Interfaces 2014; 6: 19668-19679.

[67] Okan D, Woo K, Ayello EA and Sibbald G. The role of moisture balance in wound healing. Adv Skin Wound Care 2007; 20: 39-53; quiz 53-35.

[68] Wang W, Yang C, Wang XY, Zhou LY, Lao GJ, Liu D, Wang C, Hu MD, Zeng TT, Yan L and Ren M. MicroRNA-129 and -335 promote diabetic wound healing by inhibiting Sp1-mediated MMP-9 expression. Diabetes 2018; 67: 1627-1638.

[69] Zhang T, Liu F and Tian W. Advance of new dressings for promoting skin wound healing. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 2019; 36: 1055-1059.

[70] Molan P and Rhodes T. Honey: a biologic wound dressing. Wounds 2015; 27: 141-151.

[71] Samadian H, Zamiri S, Ehterami A, Farzamfar S, Vaez A, Khastar H, Alam M, Ai A, Derakhshankhah H, Allahyari Z, Goodarzi A and Salehi M. Electrospun cellulose acetate/gelatin nanofibrous wound dressing containing berberine for diabetic foot ulcer healing: in vitro and in vivo studies. Sci Rep 2020; 10: 8312.

[72] Zhang B, Wang M, Gong A, Zhang X, Wu X, Zhu Y, Shi H, Wu L, Zhu W, Qian H and Xu W. HucMSC-exosome mediated-wnt4 signaling is required for cutaneous wound healing. Stem Cells 2015; 33: 2158-2168.

[73] Zhang J, Guan J, Niu X, Hu G, Guo S, Li Q, Xie Z, Zhang C and Wang Y. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. J Transl Med 2015; 13: 49.

[74] Perez-Panero AJ, Ruiz-Munoz M, Cuesta-Vargas AI and Gonzalez-Sanchez M. Prevention, assessment, diagnosis and management of diabetic foot based on clinical practice guidelines: a systematic review. Medicine (Baltimore) 2019; 98: e16877.

[75] Mizukami H and Osonoi S. Pathogenesis and molecular treatment strategies of diabetic neuropathy collateral glucose-utilizing pathways in diabetic polyneuropathy. Int J Mol Sci 2020; 22: 94.

[76] Shabbir A, Cox A, Rodriguez-Menocal L, Salgado M and Van Badiavas E. Mesenchymal stem cell exosomes induce proliferation and migration of normal and chronic wound fibroblasts, and enhance angiogenesis in vitro. Stem Cells Dev 2015; 24: 1635-1647.