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Innovative Wound Dressings for Diabetic Foot Treatment

INVITED REVIEW
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ABSTRACT

Diabetes-related foot ulcers lead to increased morbidity, death, and economic consequences. Diabetes-related foot disorders lead to about 1 million partial limb amputations each year. Every 20 seconds, a limb is lost somewhere in the world.

Their pathophysiology encompasses neuropathy, trauma, infection, and vascular blockage, which impair wound healing. Wound healing methodologies can be classified into conventional care interventions and advanced therapeutic approaches. Standard treatments, including debridement, offloading, and infection control, are employed in conjunction with sophisticated therapies such as negative pressure wound therapy, hyperbaric oxygen therapy, and growth factor applications. New wound dressings are being developed to help diabetic foot ulcers (DFUs) heal more quickly.

These dressings provide multiple advantages, including antibacterial characteristics, enhanced moisture retention, and expedited tissue regeneration. The following have demonstrated superior healing outcomes in DFUs: human amniotic membrane, LeucoPatch, resveratrol, bioengineered skin substitutes, microRNA-based wound dressings, and fish skin grafts. These solutions are practical and suitable for complex cases.

These improvements show potential for enhancing diabetic foot ulcer treatment; however, additional data is necessary to validate their long-term efficacy and cost-effectiveness. Innovative wound dressings should be regarded as supplementary to the optimal standard of care when the standard treatment alone has proven ineffective in healing the ulcers. Despite international diabetic foot guidelines categorizing these goods as weak recommendations supported by low to moderate evidence, there remains a continual necessity for novel strategies. These developments can substantially augment the management of DFUs by supplementing and refining current therapeutic modalities.

Keywords: Diabetes, diabetic foot ulcers, innovative wound dressings, wound healing

Introduction

Defined by the World Health Organization as "the foot of a diabetic patient that poses a potential risk of pathological consequences, including infection, ulceration, and/or destruction of deep tissues, associated with neurological abnormalities, varying degrees of peripheral vascular disease, and/or metabolic complications of diabetes in the lower limb."[1,2]

Associated with increased morbidity and mortality rates, as well as substantial financial burdens, foot ulcers are a significant complication of diabetes mellitus.[3-5] The incidence rate of diabetes-related foot ulcers is 2%, with a lifetime incidence rate that ranges from 19% to 34%.

The recurrence rate of diabetes-related foot ulcers is 40% within a year of successful healing.

As a result, the prevention of diabetes-related foot problems occurs within 1 year, and 65% within 3 years.

Consequently, the prevention of diabetes-related foot ulcers is essential for mitigating patient risk and alleviating the economic and social burden on society.[6]

About 85% of non-traumatic lower extremity amputations take place in individuals with a history of diabetic foot ulcers (DFUs). Annually, more than 1 million individuals with diabetes undergo partial or complete leg amputation due to problems associated with diabetic foot. This indicates that every 20 seconds, a limb is lost someplace globally.[7]

Presence of neuropathy, secondary infection, trauma, and vascular occlusive disease is pivotal in the pathophysiology of DFUs. Peripheral neuropathy induces intrinsic muscle atrophy, resulting in hammer toe formation and the emergence of high-pressure regions on the plantar

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surface near the metatarsal heads. Repeated stress during ambulation, along with diminished feeling and proprioception, renders the skin susceptible to injury owing to the atrophy and displacement of protective plantar fat pads. This results in ulceration and infection, particularly when there is little skin protection or poorly fitting footwear.

Avoiding skin injuries (redness, blisters) and neglecting to apply moisturizing lotions can result in ulceration and the development of invasive infections of the soft tissues. Tissue deterioration continues if not treated quickly, especially if the patient continues to walk.

Having neuropathy, a history of toe amputation, or a foot deformity significantly increases the probability of ulcers (32 times greater). In the end, the harmful consequences of injury and infection reach beyond the deep fascia, making it easier for the infection to spread to the midfoot. Half of the serious cases involving the lower extremities, joints, and tendon sheaths are caused by infections. Infections account for fifty percent of significant lower extremity amputations (above or below the knee) in diabetic individuals.[8,9]

Owing to the complicated etiology of diabetic wounds, DFUs continue to present a therapeutic difficulty. Wound healing methodologies can be classified into conventional care interventions and advanced therapeutic approaches. Standard care treatments comprise glycemic regulation, offloading, wound debridement, and infection management, whereas advanced therapies include specialized wound dressings, hyperbaric oxygen therapy (HBOT), negative pressure wound therapy, and growth factor treatments such as platelet-rich plasma, stem cells, and cell- and tissue-derived products. In light of clinical requirements, it is probable that stimulus-responsive and multifunctional therapeutic approaches that enhance diabetic wound healing will play a significant role in future diabetic wound management.[10]

The imperative to augment the efficacy of wound dressings, particularly for the management of DFUs, has posed a challenge for researchers and clinicians alike. An optimal dressing must ensure moisture equilibrium, protease absorption, stimulation of growth factors, antibacterial properties, oxygen permeability, and support for autolytic debridement to promote granulation tissue formation and re-epithelialization. Moreover, medicated systems must provide prolonged efficacy, elevated efficiency, and enhanced sustained drug release.[11]

Notwithstanding progress in wound care, the management of DFUs continues to be intricate, with numerous guideline recommendations classified as poor and substantiated by low to moderate quality evidence. Biological grafts, allografts, and xenografts can improve healing by offering a framework for tissue regeneration.[12] This review will assess advanced wound coverings created for DFUs.

MAIN POINTS

- The subject "Innovative Wound Dressings for Diabetic Foot Treatment" encompasses a range of advanced therapies and materials aimed at enhancing the healing of diabetic foot ulcers (DFUs).
- These advanced dressings aim to address the challenges related to DFUs, including extended healing durations, elevated recurrence rates, and the potential for consequences such as infections and amputations.
- Innovative wound dressings should be considered as adjuncts to the optimal standard of care when the standard treatment alone has proven ineffective in healing the ulcers.

Human Amniotic Membrane

The fresh amniotic membrane consists of fibronectin, collagen, hyaluronic acid, cytokines, growth factors, and anti-inflammatory proteins, including interleukin-1 receptor antagonist. Evidence indicates that this tissue exhibits anti-inflammatory, antifibrotic, and antibacterial characteristics. It is deemed non-immunogenic and has not been noted to provoke a substantial immunological response. These qualities are thought to be retained in cryopreserved and dehydrated amniotic membrane products, rendering it a conveniently accessible tissue with regenerative capabilities. A dehydrated amniotic membrane product has demonstrated the ability to release growth factors into saline and to promote the migration of mesenchymal stem cells, both in vitro and in vivo.[13]

The human amniotic membrane (HAM) is made up of 2 layers: the amnion and the chorion, which form the innermost region of the amniotic sac or placenta. After delivery, the membrane is cleaned and sterilized before being frozen or dehydrated for use as an allograft. Compounds from the amniotic fluid, amnion, chorion, and umbilical cord are being studied for treating various conditions, such as venous ulcers, diabetic lower extremity ulcers, plantar fasciitis, knee osteoarthritis, and ophthalmic abnormalities. These treatments are available as patches, suspensions, or particles for use as wound dressings, as well as connective tissue extracts for topical or injectable.[14,15]

LeucoPatch

Platelet-rich plasma or platelet-rich fibrin may serve as a potential treatment for non-healing foot ulcers. This method facilitates the healing of difficult ulcers in diabetic patients by enhancing tissue repair, promoting angiogenesis, and inducing the release of cytokines and growth factors associated with inflammation. The use of platelet preparations is established; however, the evidence supporting their benefits remains inconsistent. The development of multilayer patches comprising autologous leukocytes, platelets, and fibrin (Leucopatch, Reapplix ApS, Birkerød, Denmark), which can be prepared at the bedside without additives, represents a novel option. Two pilot studies, one involving participants with difficult-to-treat DFUs, have demonstrated beneficial effects on ulcer healing, with no safety concerns reported.[16]

A recent multicenter, international, observer-masked, randomized controlled trial (RCT) conducted by Game et al[16] has yielded favorable outcomes concerning the application of autologous immune cell, platelet, and fibrin patches (LeucoPatch). Patches were applied to the surface of wounds in diabetic patients and those with difficult-to-heal DFUs. The RCT was carried out in 32 specialized diabetic foot clinics located in Sweden, Denmark, and the United Kingdom. After a 4-week preparation period, patients with less than a 50% reduction in DFU size were randomly assigned to 1 of 2 groups: standard care (137 patients) or standard care with weekly LeucoPatch application (132 patients). The primary end measure was the percentage of ulcers that had complete epithelialization within 20 weeks and remained healing for 4 weeks. In the LeucoPatch group, 45 out of 132 ulcers (34%) healed within 20 weeks, while 29 out of 134 ulcers (22%) in the conventional care group healed [odds ratio (OR): 1.58, 95% CI: 1.04-2.40, $P = .0235$]. The median healing time was 72 days

(interquartile range [IQR], 56 -103 days) for the LeucoPatch group and 84 days (IQR, 64-98 days) for the standard care group ($P = .0343$). The LeucoPatch group exhibited a shorter healing time compared to the standard care group, with a hazard ratio of 1.709 (95% CI: 1.071-2.728, $P = .0246$). There were no differences seen between the 2 treatment groups in terms of major or minor amputations, clinical infections, antibiotic use, or adverse events. The incidence of unfavorable or major adverse events was similar across the 2 groups. Despite multiple venesections, individuals treated with LeucoPatch experienced constant anemic rates.

Resveratrol

Resveratrol (RV) is a polyphenolic compound found in various plants, particularly in the skin of grapes, and is known for its potential health benefits, including antioxidant properties and effects on cardiovascular health.

Resveratrol (C14H12O3: 3,5,4′-trihydroxy-trans-stilbene, RES) is a natural polyphenol classified as a phytoalexin, present in peanuts, grapes, mulberries, blueberries, and red wine. Resveratrol exhibits antioxidant and anti-inflammatory characteristics.[17]

This study is a clinical device trial that is open, prospective, and comparative in design, aimed at evaluating the effectiveness of the medical device Dermalix (Dx) for diabetic foot wounds. Dermalix is a dermal matrix characterized by a 3-dimensional collagen-laminin porous structure, further enhanced by the incorporation of RV-loaded hyaluronic acid and dipalmitoylphosphatidylcholine-based microparticles.

Cetinkalp S and colleagues compared the effectiveness and safety of the wound dressing Dx with standard wound care (SWC), which includes irrigation and cleansing with sterile saline solution, for Wagner grade 1 and 2 wounds. Forty-eight patients were randomly assigned to receive either SWC alone or SWC in conjunction with Dx. A 4-week treatment period was followed by a 2-month follow-up without intervention. Total collagen, vascular endothelial growth factor, tumor necrosis factor, interleukin 1, caspase 3, glutathione, reduced/oxidized glutathione, lipid peroxidation levels, and wound area measurement were all evaluated.[18]

After 4 weeks, wound closure percentages were recorded at 57.82% for the Dx group and 26.63% for the SWC group. Dermalix significantly decreased levels of tumor necrosis factor, caspase 3, and reduced/oxidized glutathione. Dermalix was found to double the rate of wound healing and decrease oxidative stress. The application of Dx in the initial stage of wound treatment was found to facilitate faster healing and enhance safety profiles.[18]

Resveratrol enhances endothelial function and exhibits significant pro-angiogenic properties, making it a potential treatment for diabetic foot wounds. Pandey et al[19] developed a liposome-in-hydrogel system containing RV to enhance the healing of DFUs. The thin-film hydration method was employed to prepare RV-loaded liposomes. The RV-loaded liposomal gel enhanced skin penetration. The effectiveness of the developed formulation was evaluated using an animal model of diabetic foot ulcers. The application of the formulated product notably decreased blood glucose levels and enhanced ulcer healing and wound closure by day 9 through the elevation of glycosaminoglycans. In the wound area, there was an observed increase in re-epithelialization speed, fibroblast proliferation, collagen formation, and a decrease in inflammatory cell infiltration.

Bioengineered Skin Substitutes

Over the past 10 years, tissue engineering has progressed markedly, resulting in the development of alternative wound care approaches, including bioengineered skin substitutes. Bioengineered skin and soft tissue substitutes may originate from human tissue (either autologous or allogeneic), non-human tissue, synthetic materials, or a combination thereof. Bioengineered skin substitutes possess significant potential to enhance the healing of DFUs and support tissue regeneration. They offer structural support for cellular growth and proliferation, modulate immune responses, promote angiogenesis, and stimulate tissue regeneration. The management of non-healing diabetic lower extremity ulcers that fail to respond sufficiently to one month of standard ulcer treatment, including tissue engineering or amniotic skin substitutes, may be deemed medically necessary.[20,21]

Bioengineered skin substitutes are laboratory-created skin analogs that exhibit certain biological and pharmacological properties similar to those of human skin.[22]

Bioengineered skin and soft tissue substitutes may be classified as acellular or cellular. Acellular products, such as skin with removed cellular material and synthetic substitutes, are made out of a matrix or framework comprising collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix products vary in species (human, bovine, porcine), tissue origin (e.g., skin, pericardium, intestinal mucosa), additives (e.g., antibiotics, surfactants), hydration state (wet, freeze-dried), and preparation requirements (multiple rinses, rehydration).[23]

Cellular products comprise live cells, including fibroblasts and keratinocytes, embedded within a matrix. The cells within the matrix may originate from autologous, allogeneic, or alternative species, such as bovine or porcine sources. Skin substitutes can include dermal cells, epidermal cells, or a combination of both, and may deliver growth factors to enhance the healing process. Bioengineered skin substitutes serve as either temporary or permanent wound coverings.[24]

Bioengineered skin substitutes are primarily categorized according to their structural layers and cellular composition. The primary categories are as follows:[23,22]

1. Acellular monolayer: a dermal layer derived from allogeneic or animal sources that lacks live cells, serving as a scaffold for the colonization of host cells. Examples include Allopatch®, Oasis®, GraftJacket™, DermaCELL®, MatriStem®, and Primatrix®.
2. Cellular monolayer: a dermal layer derived from allogeneic or animal sources, lacking viable cells and enriched with neonatal fibroblasts. Examples include Dermagraft® and Hyalograft® 3D.
3. Acellular bilayer: a dermal layer derived from allogeneic or animal sources that lacks live cells, serving as a scaffold for host cell colonization, and is covered by a synthetic acellular epidermal layer. Examples include Integra® DRT.
4. Cellular bilayer: a dermal layer derived from allogeneic or animal sources, lacking viable cells, enriched with neonatal fibroblasts, and covered by an epidermal layer consisting of neonatal keratinocytes. Example: Apligraf®.

A meta-analysis by Primous et al[23] involved systematic searches in PubMed, Cochrane Library, and Web of Science, resulting in the identification of 1312 articles, with 24 selected for qualitative analysis. The

results demonstrate that bioengineered skin substitutes produce superior outcomes relative to conventional wound care methods. Bioengineered skin substitutes demonstrated superiority in wound closure time and rate, although they were associated with higher costs. The meta-analysis indicates that bioengineered skin substitutes show potential for treating diabetes-related foot ulcers; however, further research is required.

MicroRNA-Incorporating Wound Dressings

Small non-coding RNA molecules known as microRNAs (miRNAs) have recently been shown to regulate inadequate wound healing and could be useful therapeutic targets for DFUs. MicroRNAs therapeutics may be delivered to the wound area using various systems, such as exosomes and nanoparticles. Wound dressings demonstrate considerable potential for treating diabetic wounds via the sustained topical delivery of specific miRNAs. Numerous miRNAs have been recognized as regulators at different phases of wound healing, and their altered expression may contribute to the development or treatment of chronic wounds, especially diabetic ulcers.[24] MiR-155 is expressed during the inflammatory phase and promotes the synthesis of cytokines and growth factors. Inhibition of miR-155 leads to reduced inflammatory responses, diminished immune cell accumulation at the wound site, and improved healing outcomes.[25]

MiR-31 levels are markedly increased in keratinocytes in the wound periphery during inflammation and proliferation, promoting re-epithelialization and wound closure.[26]

MiR-126 was raised in diabetic patients with DFUs and is essential for wound healing by facilitating angiogenesis and the formation of vascular networks.[24]

Wound dressings containing bioactive agents infused with nanoparticles, such as miRNA-tagged nanoparticles, are a promising approach for improving the healing of diabetic wounds. Sener and colleagues created a self-healable, flexible, injectable, zwitterionic cryogel with anti-adhesive characteristics, integrating miR-146a linked cerium oxide (CNP) nanoparticles to improve wound healing in a homozygous diabetic mouse model. Non-toxic nanoparticles can reduce reactive oxygen species. The prolonged release of miR-146a as an anti-inflammatory miRNA led to reduced levels of IL-6 and CXCL2, accompanied by an elevation in type 1 collagen. The findings demonstrate that the wound healed 6 days sooner in the CNP-miR-146a conjugate-treated group than in the control zwitterionic gel-treated group, subsequent to the topical application of the miRNA-loaded gel.[27]

In a diabetic rat model, studies show that chitosan hydrogel supplemented with exosomes from synovial mesenchymal stem cells overexpressing miR-126-3p significantly promotes wound closure through facilitating re-epithelialization, granulation, and angiogenesis by day 14 compared to cells that were left untreated or were only treated with chitosan.[28]

The difficulties related to chronic wound healing require the discovery of innovative methods to expedite wound closure. The continuous release of miRNAs using appropriate wound dressings, such as chitosan hydrogel or nanofibers filled with therapies like miRNA-modified exosomes, offers a potential strategy for the healing of diabetic chronic wounds. The investigation of miRNAs in wound dressing is still in its initial stages. Consequently, both preclinical and clinical investigations are crucial to substantiate miRNA-based therapeutic applications.[29]

Fish Skin Graft

Dardari et al[30] demonstrated that intact fish skin grafts from Atlantic cod facilitated faster and more effective healing in patients with deep and diabetic penetrating foot ulcers when compared to conventional wound care methods. The researchers performed a multicenter clinical study across 15 tertiary care centers with diabetic foot units in France, Italy, Germany, and Sweden to assess the efficacy and safety of intact fish skin grafts versus standard care practices in treating complex DFCs.

A study involving 255 diabetic patients aged 18 and older with lower extremity wounds penetrating the tendon, capsule, bone, or joint compared the efficacy of intact fish skin grafts to SWC over a duration of 14 weeks. The main outcome measure was the proportion of wounds achieving complete closure within 16 weeks. Wound healing was evaluated at 20 and 24 weeks. The findings indicated that the wound healing rate at 16 weeks was significantly greater for intact fish skin grafts than for standard care (44.0% vs. 26.4%, adjusted odds ratio [aOR], 2.58; 95% CI, 1.48-4.56). Fish skin grafts demonstrated superior effectiveness relative to SWC practices at both 20 weeks (aOR, 2.15; 95% CI, 1.27-3.70) and 24 weeks (aOR, 2.19; 95% CI, 1.31-3.70). The average healing duration was 17.31 weeks for the intact fish skin graft group and 19.37 weeks for the standard care group. Intact fish skin grafts demonstrated quicker healing times relative to SWC, with a hazard ratio of 1.59 (95% CI, 1.07-2.36). Target wound infections represented the most prevalent adverse effect, occurring in a comparable number of patients across both groups.[30]

The findings of Dardari et al indicate that intact fish skin grafts could serve as an effective treatment for DFUs, promoting wound closure and possibly decreasing the likelihood of additional complications. The findings align with earlier trials of less severe ulcers, which demonstrated comparable positive outcomes with fish skin grafts. Fish skin grafts demonstrate effectiveness similar to advanced wound healing methods, including total contact casting and HBOT, yet they may offer greater practicality owing to their ease of application. The trial's observed accelerated wound healing rates are promising for mitigating complications related to delayed wound healing in DFUs. Additional research is required to determine the long-term effects of fish skin grafts, particularly in relation to recurrence prevention and the assessment of cost-effectiveness.[31]

Conclusion

Innovative wound dressings are being developed to improve the healing of DFUs. The HAM exhibits potential owing to its anti-inflammatory, antimicrobial, and regenerative characteristics. LeucoPatch, a platelet-rich plasma patch, demonstrates efficacy in enhancing wound healing in difficult-to-treat ulcers. Resveratrol, a polyphenolic compound characterized by its antioxidant and anti-inflammatory properties, is under investigation for its potential to enhance wound healing, mitigate oxidative stress, and promote endothelial function. Bioengineered skin substitutes represent a novel approach in wound care, offering structural support for cellular proliferation and facilitating angiogenesis. Substitutes may be classified as acellular or cellular, possessing the capacity to improve tissue regeneration and facilitate wound closure. A promising approach involves miRNA-based wound dressings that regulate wound healing by targeting specific cellular

processes such as inflammation and angiogenesis. Fish skin grafts have shown improved healing outcomes in DFUs, providing an effective solution for complex cases.

These innovations show potential for enhancing the treatment of DFUs; however, additional research is required to validate their long-term effectiveness and cost-efficiency.

International diabetic foot guidelines currently classify these products as weak recommendations based on low to moderate evidence; however, there remains a necessity for innovative approaches. These innovations can substantially improve the management of DFUs by augmenting and refining current treatment approaches.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

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Author Contributions: Concept – Ş.Ç.; Literature Search – Ş.Ç.; Writing – Ş.Ç.; Critical Review – Ş.Ç.

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