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Review Article:

Principle and New Strategies in Diabetic Foot Management

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Abstract

Background: Diabetic foot ulcers (DFU) occur in up to 15% of all diabetic patients and are a leading cause of nontraumatic amputation worldwide. DFUs require identifying the etiology and assessing the co-morbidities to provide the correct therapeutic approach, essential to reducing lower-extremity amputation risk. The high rates of therapy failure have resulted in the development of new therapies. **Aim:** Highlight the current trends in DFU management that could replace or complement the classical strategy for the management of DFU, as well as selective and targeted strategies that are needed to improve the healing process. **Method:** The authors, with precision, conducted an exhaustive literature search by thoroughly exploring the Science Direct, Scopus, PubMed, and Web of Science databases. They specifically sought out published studies and original articles that were featured in esteemed peer-reviewed journals and reported on original research. **Conclusion:** These new techniques are promising but still mostly unproven. New and generally more expensive therapies should be seen as adding to traditional approaches and not a replacement for conventional approaches.

1. Introduction

Diabetic foot ulcer (DFU), which is characterized as a foot ulceration linked with peripheral artery disease, neuropathy, or both in a diabetic patient, is one of the most serious and debilitating consequences of diabetes Within the diabetic population, 4 –10% of cases are diabetic foot ulcers. Once DFU has developed, there is a heightened risk of ulcer progression that may ultimately lead to amputation. Shockingly, the rate of lower limb amputation in patients with diabetes is 15 times higher than in patients without diabetes. It is estimated that approximately 50%-70% of all lower limb amputations are caused by DFU (1).

DFUs are caused by a variety of pathogenic mechanisms; therefore, managing them calls for an interdisciplinary, multimodal strategy that focuses on three key areas: (1) prevention, (2) addressing the several mechanisms that lead to the creation of DFUs, and (3) promoting wound healing. New treatments are therefore required that address all aspects of DFU wound care, such as ulceration avoidance and wound healing promotion (2).

The majority (60–80%) of foot ulcers will heal, while 10–15% of them will remain active, and 5–24% of them will finally lead to limb amputation within a period of 6–18 months after the first evaluation. Neuropathic wounds are more likely to heal over a period of 20 weeks, while neuroischemic ulcers take longer and will more often lead to limb amputation (3).

Apart from the medical consequences, diabetic ulcers entail significant financial expenses. In addition to the cost of managing diabetes alone, the United States (US) pays medical expenses of between US$9 to US$13 billion for the treatment of diabetic foot disease (4).

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2. Etiology

A DF typically develops when several circumstances come together, including peripheral vascular disease and an initial insult (trauma) that the patient is unaware of due to pre-existing neuropathy beside an infection which is frequently the cause of a DFU, and if left untreated, it can lead to amputation of the lower leg entirely or in part (5). The three common underlying causes are:

2.1. Diabetic Peripheral Neuropathy

Neuropathy is a neurological condition that impairs feeling, and mobility, and causes other aspects of health based on the site of the injured nerve. One of the primary causes of foot ulcers in diabetics is peripheral neuropathy (6). Diabetic Peripheral neuropathy (DPN) in the lower extremities affects up to 66% of diabetic individuals (7). Research has shown that neuropathy is caused by metabolic problems brought on by hyperglycemia which are elevated levels of intracellular advanced glycated end products, activation of protein kinase C, increased hexosamine pathway flux, and polyol pathway (8).

Motor neuropathy can cause atrophy, and deformities in the toes, affecting small muscles of the foot and thus diminished joint movement. At the same time, autonomic neuropathy raises body temperature and decreases sweating. When combined, they can result in skin cracking, and inflammation, which can all lead to the formation of a DFU (9).

2.2. Peripheral Arterial Disease (PAD)

The end products of advanced glycation are produced by hyperglycemia and oxidative stress, and they have a role in the development of microvascular and macrovascular problems in individuals with diabetes mellitus (10). The vascular disorder known as peripheral artery disease (PAD) is characterized by lower extremity atherosclerotic occlusive disease, which thickens the capillaries and reduces their flexibility, resulting in ischemia (9). Although PAD by itself does not cause a DFU, it can exacerbate injuries caused by the combination of multiple risk factors, including trauma, infection, dry skin, foot abnormalities, and DPN (11).

2.3. Infection

When a DFU appears, it is susceptible to the onset of infections, mainly owing to prolonged environmental exposure of the wound; pathogen-related factors such as density, virulence, and interactions; and immune defects linked to the host including (1) reducing the patient's immunity via lowering inflammatory cell production (2) delayed tissue healing (by altering the amount of collagenase and growth factors secreted); (3) promoting bacterial development since it prefers an environment with high glucose levels (12) and (4) hyperglycemic state seems to impairs the body's capacity to react to antibiotic medication (13).

Infections in DFUs further aggravate the wound healing process, being responsible for frequent visits to the hospital and constituting the main complication that leads to non-traumatic amputations of lower limbs in patients with DM. An infected foot ulcer accounts for ~60% of lower extremity amputations, making infection perhaps the main proximate basis of this tragic outcome. In a large prospective study of patients with DFU, the existence of infection augmented the risk of a minor amputation by 50% compared to ulcer patients without infection (14).

3. Classification

Types of diabetic foot ulcers According to Edmon diabetic foot ulcers are divided into 2 groups, namely:

3.1. Neuropathic ulcers

Feet are warm, perfusion is still good with pulsation still palpable, perspiration is reduced, and skin dry and cracked
(15).

3.2. Neuro-ischemic ulcers

Feet are colder, not palpable pulsation, thin skin, smooth and without hair, subcutaneous tissue atrophy, intermittent claudication and rest pain may not be present due to neuropathy (15).

4. Diabetic foot management

The proper stage and severity classification is essential for the management of DFUs. Focusing on diabetes mellitus (DM) management in addition to wound care, appropriate infection control, pressure relief, and blood flow optimization are all important aspects of providing DFUs with adequate care (16).

4.1. Peripheral Neuropathy

The management of diabetic neuropathy is still inadequate despite the disease's personal and societal costs. This is partly because the illness is inherently complex and unexpected, and there has not been any systematic testing for diagnosis. In addition, current DPN therapy mostly addresses symptoms rather than the underlying autonomic nerve deficiency (17).

Optimizing glycemic control is still seen as a crucial initial step in delaying the development of diabetic neuropathy. In a large cohort of over 3,000 persons with type 1 diabetes, the Eurodiab Insulin-Dependent Diabetes Mellitus (IDDM) study discovered a link between inadequate glycemic control and the development of DPN. However, as strict glycemic control may raise mortality in diabetic neuropathy patients, it should be used with caution (18). Pancreas

transplantation is the only known treatment to reinstate insulin secretion in diabetic individuals. Numerous studies have shown that patients with DPN who had pancreatic transplantation experienced improvements in their motor and sensory neuropathy (19).

Other pharmacological treatments approved by the Food and Drug Administration (FDA) for the treatment of diabetic neuropathy include pregabalin, duloxetine, tapentadol, and topical capsaicin (20), they treat symptoms of diabetic neuropathy, although they are not specifically approved to treat the condition. Peripheral nerve injury can be prevented or reversed by alpha-lipoic acid (ALA). It is a scavenger of free radicals that reduces oxidative stress, which prevents ischemic nerve injury. Although it is used to treat DPN in many nations, the US and the UK do not have regulatory approval for it (21).

4.2. Revascularization

If ischemia symptoms or signs appear in diabetic patients with foot ulcers, healing will be significantly impeded. This is a sign that revascularization is necessary to promote DFU healing and prevent or postpone amputation.

When a patient has an ankle pressure of fewer than 50 mmHg or an ankle-brachial index (ABI) of less than 0.5, revascularization should be investigated. If transcutaneous oxygen pressure TcpO2 is less than 25 mmHg or the toe pressure is less than 30 mmHg, revascularization should also be taken into consideration. For patients who have significant tissue loss or infection, physicians may, however, think about revascularization at higher pressure points.

In addition, regardless of the outcomes of the vascular diagnostic tests mentioned above, revascularization should be considered if an ulcer does not exhibit healing after six weeks of optimal care (22). Revascularization can be carried out by open bypass or endovascular technique. According to recent research, bypass surgery may be less invasive and more effective than endovascular surgery (23).

The angiosome idea is a novel approach that has been researched recently to improve results following revascularization treatments. A source artery supplies an angiosome, which is anatomically composed of skin, subcutaneous tissue, fascia, muscle, and bone and is drained by an intended vein. From that perspective, it is reasonable to assume that improved wound healing and limb salvage rates could arise from the revascularization of the source artery to the angiosome (24).

4.3. Treatment of infection

Any foot wound in a diabetic patient should be regarded as potentially infected, especially if the patient has a history of foot wounds or amputations, peripheral neuropathy, vascular disease, or a wound that tests positive for infection on probe-to-bone testing (25).

Broad-spectrum antibiotics are usually given first during regular treatment, then, after the results of the bacterial culture are known, a more specific antibiotic is used. Broad-spectrum antibiotics that are most frequently employed include carbapenems β-lactam or β-lactamase inhibitor combination, like ampicillin/sulbactam, ticarcillin/clavulanic acid, and piperacillin/tazobactam (26).

Oral antibiotics that target Staphylococcus and β-hemolytic streptococci are suggested as a first line of treatment for superficial ulcers with mild infections. In a patient with a deep or possibly life-threatening infection, it is critical to start empiric, intravenous, broad-spectrum antibiotic therapy against common gram-positive and gram-negative bacteria (27). Current guidelines state that cefoperazone/sulbactam or piperacillin/tazobactam with clindamycin are the empirical antibiotics of choice for DFU infection; if the culture's sensitivity report justifies it, an escalation to carbapenem with teicoplanin is advised (28).

Methicillin-resistant Staphylococcus aureus (MRSA) infections are treated with empirical therapy if the patient has a history of infection, if MRSA infections are common in the community, or if the illness is resistant to conventional treatment. Vancomycin is the most commonly used medication to treat MRSA, but due to a 50% rise in reports of antibiotic resistance, linezolid is now utilized as an alternative (26). Metronidazole is the preferred treatment for anaerobic bacteria found in foot ulcers with ischemia and deep tissue necrosis (29). The IDSA advises taking antibiotics for one to two weeks for mild infections and for two to three weeks for moderate-to-severe infections; however, once the clinical signs and symptoms of an infection resole antibiotics can be stopped, instead of continuing them until the wound is healed. Surgical debridement is necessary for chronic osteomyelitis before antibiotic therapy can be started (25).

4.4. Off-loading

For diabetic neuropathy patients, elevated dynamic plantar pressures (PPs) nearly triple or quadruple the chance of developing foot ulcers. The process of improving healing at the site of ulceration by reducing pressure or "load" by surgery or other devices is known as "off-loading." (30).

Total contact casts (TCCs), which are thought to be the "gold standard" for protecting and off-loading DFUs, are made of cast that is formed to closely resemble the foot and ankle's anatomical features to restrict mobility inside the cast. After that, an exterior layer of fiberglass cast material is placed (31).

Among the alternative treatments are detachable cast boots (RCBs), Patients prefer them since they may be removed to perform daily activities. However, clinical trials using TCC showed faster healing rates. due to force adherence.

The most common problem related to using TCCs, patients may not find wearing a TCC acceptable, and it becomes challenging to go about regular tasks and may cause pain in the hips and knees, particularly in people who already have arthritis, and they should not be used for heel ulcers (32).

Additional off-loading interventions include the use of cushioned dressings, postoperative sandals, therapeutic shoes with special insoles (commonly referred to as "diabetic shoes"), and postoperative shoes or sandals (30). These off-loading strategies are the least effective but have the benefit of being widely accepted by patients. They can be used as artificial shock absorbers to reduce the risk of foot ulceration by offering an extrinsic protective and accommodative mechanism, as well as to prevent recurrence (33).

Newly developed Intelligent plantar pressure offloading shoes by the team at the University of Geneva, Switzerland with an auto-contouring insole that reads plantar pressures (PPs) continually and adjusts its shape in the heel and forefoot to redistribute high- pressure points. The footwear is made to look like a regular shoe that patients would use daily to increase adherence. This intelligent plantar pressure offloading system shows promising outcomes for the future development of diabetic foot ulcer prevention and treatment while improving patient adherence to the ultimate goal of preventing lower limb amputations (34).

4.5. Debridement

Debridement is the process of removing diseased materials and necrotic and dead tissues from a wound to reduce the overall number of bacteria present and promote the synthesis of growth factors. In addition, this technique lowers pressure, assesses the wound bed, and promotes wound drainage. The healing process improves with increased debridement frequency (35).

Surgical, enzymatic, autolytic, mechanical, and biological debridement are among the several types of debridement (**Table 1**). Surgical debridement has been demonstrated to be a more effective approach for DFU healing among various techniques. This kind of debridement is primarily intended to induce an acute ulcer from a chronic one. To promote ulcer healing, surgical debridement should be performed as frequently as necessary if new necrotic tissue keeps forming (36). Despite the advantages of debridement, it should always be followed by the application of topical wound healing agents, dressings, or wound closure procedures, which may be expensive (37).

Table 1. The several types of debridement

Method	Explanation	Advantage	Disadvantage
Autolytic	Use moisture-retentive dressings to facilitate the natural breakdown of necrotic tissue by endogenous phagocytic cells and proteolytic enzymes, which can eventually cause the necrotic tissue to soften and separate from the wound bed.	The process is extremely selective, affecting only necrotic tissue.	Takes a few days (38).
surgical	Surgical excision is performed on all necrotic tissue until either bleeding tissue is exposed or only healthy tissue is left.	Turn a chronic ulcer into an acute one.	Require surgical skill (39).
sharp	Using a scalpel or pair of scissors, tissue is cut in layers up to the point where viable tissue is still present.	Quick, simple and not expensive compared to surgical debridement in the theatre.	It can be painful when slough or eschar is pulled on viable tissue during treatment to facilitate removal.(40).
Biological (Larval therapy)	Biologically debrides the wound bed by breaking down dead tissue, consuming and killing microorganisms, and accelerating the formation of fibroblasts to promote wound healing.	Rapid, selective.	Raises unit costs and might not be well-accepted by certain patients(41).
Enzyme	Enzyme preparation mainly two enzymes: streptokinase (which dissolves fibrin clots) and streptodornase (which liquefies pus cells) (42)	Selective and painless method.	Potential for antigenic reaction in patients receiving streptokinase for thrombolysis after myocardial infarction or after receiving it beforehand (40).
Mechanical	a soft polyester fiber pad that is intended for one use and is softly wiped over the wound to remove exudate, dead cells, and wound debris. (43).	Fast (2-4 in)	painful and selective (41).

5. New strategies

5.1. Tissue engineering approach

design tissue replacement for traumatized tissue, requires biomaterials or organotypic structures for implantation, besides the bioreactors to grow large amounts of genes, cells, or organotypic tissue (**Figure 1**) (44).
Two primary methods, in vitro and in vivo, have been employed for the development of engineered tissue. the in vitro technique that looks to grow organs in bioreactors or tissue culture for transplantation in place of damaged or diseased tissue. The in vivo method, on the other hand, aims to develop an acellular biomaterial with indicators that facilitate tissue cell migration into the biomaterial and stimulate cell differentiation to build the necessary tissue (45).

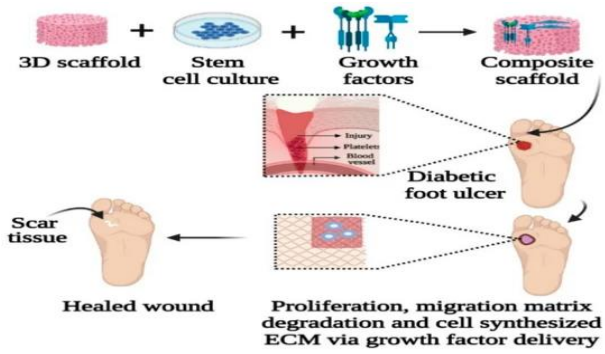

Figure 1. Biomaterial and growth factor incorporated stem cell therapy in the diabetic foot ulcer treatment (46).

The bioactive function may be a cell-binding activity, growth factor activity, growth factor-binding activity, enzymatic activity, or enzyme-binding activity. The main sources for the generation of dermal and epidermal substitutes are differentiated human cells, fibroblasts, and keratinocytes, respectively. These cells provide growth factors, signaling molecules, and extracellular matrix (ECM) proteins to the injured area to promote healing (47). Fibroblasts and keratinocytes communicate with one another to promote cell migration and maintain skin homeostasis—both of which are necessary for full wound healing (44).

Due to a shortage of donor locations, the use of autologous skin cells for wound healing is restricted (48). Instead, stem cells (SCs) have become a viable option for healing damaged tissue because of their ability to self-renew, their potential for differentiation to many cell types, and the fact that they can be extracted from a variety of tissues, including adult, fetal, and embryonic tissues (48). On the other hand, tumor formation capacity. In addition, the potential for stem cells to differentiate into the incorrect type of tissue is another issue that needs to be carefully considered before using therapeutic stem cells (48).

Many fabrications designed for implantation have a bioactive and a biopolymer backbone, regardless of whether they include cells or not. Bioactives are chosen to induce tissue cell migration, proliferation, and eventually differentiation. Biopolymers offer mechanical support for cell movement and proliferation. Nevertheless, these hydrogels and scaffolds made from the natural extracellular matrix (ECM) might offer extra biological cues to promote tissue and cell function. (49).

In addition, mechanical forces play a role in cell differentiation. Cells sense and react to substrate mechanics through an active tactile sensing system (50). Additionally, mesenchymal stem cells generated from circulating human bone marrow, are highly sensitive to the mechanical characteristics of the extracellular matrix (ECM), resulting in distinct differentiated phenotypes depending on matrix stiffness (51). Tissue engineering techniques for wound repair would necessitate the optimization of both biological and mechanical effectors because these processes are vital to wound healing.

5.2. Nanotechnology

Platforms for nanotechnology have shown new potential and advantages in the area because of their unique qualities (52). Advances in nanotechnology have created novel opportunities for delivering drugs, involving the administration of biomolecules that can be used to treat chronic wounds, such as Growth factors or DNA/RNA. Their small size and unique physicochemical characteristics enable the delivery of these medications or biomolecules into cells, shield them from deterioration, and improve the penetration of the drugs into the wound. As a result, it enables topical administration and extends the half-life of these drugs, thus lowering the number of treatments and expenses. Additionally, the encapsulation of medications and biomolecules inside nanocarriers can create different drug release patterns that might correspond with the wound healing needs (**Figure 2**) (53).

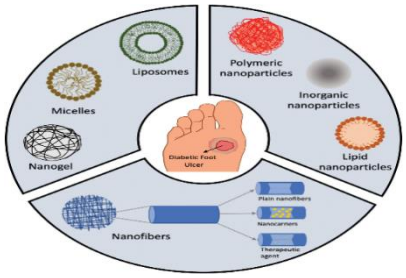

Figure 2. Schematic representation of nanocarriers used for chronic wound healing: self-assembled nanocarriers (liposomes, micelles, nanogels), Nanoparticules (NPs) (polymeric, inorganic, lipid), and nanofibers (plain and encapsulating nanocarriers or therapeutic agents). NP, nanoparticle (54).

- *Nanoparticles (NP)*

Antibacterial capabilities of metallic nanoparticles (NPs) formed from silver, copper oxide, gold, iron oxide, zinc oxide (ZnO), and aluminium oxide have been revealed. Their activity is brought on by the generation of reactive oxygen species (ROS) and interactions with bacterial enzymes, RNA, and DNA, which collectively cause bacterial death (55).

Silver nanoparticles (AgNPs) are likely the most used NPs in wound healing due to their antibacterial, anti-inflammatory, and wound-healing characteristics (56). Furthermore, no signs of toxicity or bacterial resistance were found. AgNPs have been formulated as gels, including hyaluronic and others, which have demonstrated their effectiveness in reducing the number of bacteria and treating diabetic wounds. For instance, Shi et al. created hydrogels from thiolated chitosan impregnated with AgNPs and dextran grafted with maleic acid. Wounds treated with AgNPs have demonstrated extensive collagen deposition, which may hasten the healing process (57).

Because of the exceptional antibacterial properties of Copper NPs (CuNPs), it has been the subject of much research and has been shown to have the capacity to suppress a broad range of bacterial types (58). Antibacterial properties arise from released Cu^{2} , which disrupts membranes and cell walls by changing the activity of an enzyme or stiffening the protein structure. This is followed by cytoplasmic disintegration and ultimately bacterial death. Furthermore influences the production of the hypoxia-inducible factor (HIF-1a) and controls the release of VEGF. In addition, CuNPs promote angiogenesis and aid in the healing of wounds (59).

Zinc oxide nanoparticles (ZnO NPs) are inorganic antibacterial agents used in wound-healing applications. Zinc is a long-lived element in living cells that is important for wound healing, particularly in delayed wound healing and burns (60, 61). ZnO NPs' capacity to rupture bacterial cell membranes is what determines their antibacterial action. Balaure et al. have demonstrated that a wound dressing containing collagen, ZnO NPs, and 1% orange essential oil exhibits faster wound closure and high biocompatibility in both vitro and in vivo bacterial growth inhibition (62).

Gold nanoparticles (AuNPs) are biocompatible and are extensively used in tissue regeneration, targeted drug delivery and wound healing. Gold nanoparticles do not possess any antibacterial activity when used alone Therefore, for AuNPs to be used for biological purposes, they need to be integrated with other biomolecules (ex; collagen). These modified AuNPs showed characteristics including biodegradability and biocompatibility; as a result, they may be widely used in wound healing (63).

- *Nanofiber*

Wound dressings made of nanofibers typically have a diameter of less than one micrometer and resemble those of extracellular matrix (ECM), which makes them perfect for cell attachment and development as well as the healing process (64). Its enormous surface area also helps in the incorporation and transportation of bioactive components, such as growth factors and medications. Furthermore, Nanofiber wound dressing has a high absorption capacity, which enables it to absorb excess exudates from the wound, creating a moist environment for wound healing. Consequently, materials made of electrospun nanofibers are thought to be among the greatest for dressing wounds. The majority of nanofibers were created using natural chitosan, gelatin, hyaluronic acid (HA), and alginate, or synthetic poly(-esters) such as poly-lactic acid, polyglycolic acid, and poly-lactic-co-glycolic acid (65).

Wound dressings or delivery vectors use polymeric nanoparticles owing to their antibacterial and pro-wound healing properties . Polymer-associated nanocomposites are generally more effective than polymer itself for wound-healing applications. According to Hajji et al., the chitosan-polyvinyl alcohol-Ag NP nanocomposite shown better antibacterial and antioxidant qualities than the chitosan polymer alone .

- *Liposomes*

Liposomes hold great promise as topical drug delivery systems because they facilitate the diffusion of therapeutic agents into bacterial cells. Furthermore, it has a negative charge; therefore, the liposome can inhibit bacterial growth and biofilm formation more efficiently with the bacterial cell membrane carrying the positive charge. Liposome-based carriers can be tailored to alter the lipid bilayer's shape, making them highly biocompatible and immunogenicity-free. Moreover, liposomes can be modified and inserted into bandages to provide therapeutic chemicals to the injured area continuously and sufficiently to kill germs (66, 67).

5.3. Gene therapy

Gene delivery may provide a transient or permanent modification of cellular physiology, which might then initiate a chain reaction or selectively fix malfunctioning processes to enhance and expedite the healing process. DNA stability is the main benefit of gene therapy over growth factor therapy, while growth factor prematurely broke down in the chronic wound's proteolytic environment (68).

It is possible to transfer genes to target tissue using either an ex vivo or an in vivo method. Selective cells are isolated and grown, transfected in vitro, and then transplanted into a host as part of ex vivo procedures. Compared to in vivo methods, which transfer genes directly into the target tissue without the requirement for cell culture, this approach is more expensive and labour-intensive.

The most basic type of nonintegrating expression vector is the naked plasmid. However, because of a relatively significant anionic charge in the DNA, uptake by cells is problematic. Moreover, plasmid DNA's (pDNA) vulnerability to quick clearance. Therefore, physical techniques like

electroporation, whose principles are based on the temporal increase in permeabilization of cell membrane upon application, aid in the transfer of pDNA into the tissues or cells (69, 70).

5.4. Peptide therapy

Endogenous host defense peptides also referred to as antimicrobial peptides (AMPs), are a class of peptides that are naturally present in the innate immune systems of various species and act as a first line of defense against illnesses brought on by a wide variety of bacteria. Based on their fundamental structures and topologies, these peptides are categorized into many groups, such as dermcidin, cathelicidin antimicrobial peptide (LL-37), and human endogenous β-defensins (hBDs) (71).

AMP has a cationic charge, which causes them to initiate electrostatic contacts with negatively charged phospholipid in the bacteria's cell wall and consequently mediate disruptive effects on bacteria's cell membrane and ultimately cause bacterial death.

However, AMPs can also influence the host immune system by increasing the production of cytokines and chemokines. In addition, it encourages wound healing and re-epithelization by stimulating cell migration and proliferation (72). Furthermore, they can promote angiogenesis by up-regulating angiogenic proteins and inducing the development of endothelial cells (73). Additionally, they can boost the production of extracellular matrix, increase fibroblasts' ability to contract by causing fibroblast-to-myofibroblast differentiation. and improve wound healing by raising fibroblasts' expression of α-smooth muscle actin (74).

Under some circumstances, such as diabetes, their expression levels and/or activity may change, which could result in insufficient infection control and hinder wound healing. Thus, they have been thoroughly studied in recent years and they are a good target for the treatment of diabetic foot. Some of them are now undergoing clinical studies (75). In addition to their anti-biofilm characteristics, AMPs have demonstrated encouraging outcomes in the management of DF infection. For instance, the natural peptide esculentin-1 demonstrated biofilm eradication against Pseudomonas aeruginosa strains in vitro, which is comparable to colistin's biofilm eradication capabilities (76).

However, to achieve anti-polymicrobial and wound-healing properties of AMPs for applications in wound management, we should introduce chemical changes and/or utilise cutting-edge delivery methods to improve AMP targeting, extend their duration of action at the wound site, decrease cytotoxicity, and boost stability or biocompatibility. In vitro, collagen functionalized with LL-37 or its derivatives retained low cytotoxicity and antibacterial activity (77). In a mouse wound model, chitosan hydrogel encapsulation of LL-37 induced efficient wound repair with enhanced biocompatibility (78). To improve the features of AMPs—which have shown to be promising methods for treating non-healing infected DFUs—many authors have been creating and implementing delivery systems. Indeed, these mechanisms protect AMPs from the host's diabetic microenvironment, protease breakdown, and serum inactivation; they also lessen the AMPs' intrinsic toxicity and enhance their targeting and extended delivery.

5.5. Photobiomodulation therapy (PBM)

The US Food and Drug Administration has approved low-level laser therapy (LLLT), also known as low-intensity laser therapy (LILT) or low-energy photon therapy (LEPT). It can be used as adjuvant therapy with other diabetic wound treatments. It has been shown to considerably reduce the time it takes for wounds to heal by photoactivation of cellular processes. The effects of low-level laser therapy (LLLT) are photochemical rather than thermal, and they promote the process of tissue repair by providing a low energy density that is high enough for the target cell to utilize the energy to stimulate its membrane or organelles (79).

The cytochromes in the mitochondria absorb the laser radiation, which the cell then uses to produce energy (ATP). which enters a photo-bioactivated state, A higher rate of extracellular matrix production, collagen synthesis, fibroblast proliferation, macrophage stimulation, and other effects of photostimulation that may affect wound healing have been documented in vitro (80).

Researcher Feitosa et al. conducted a randomized controlled trial in which participants with uncontrolled diabetes and diabetic foot ulcers showed a statistically significant decrease in wound size and pain levels at 12 and 30 days of low-level laser therapy as compared to groups receiving standard wound care practices (80).

On the other hand, Intense Pulsed Light (HILT) has demonstrated a beneficial
effect on wound healing in diabetic rats. The primary advantage of HILT over LLLT is that it can stimulate the deep tissue in a short period (81).

In recent years, the use of this innovative phototherapy technology in wound healing has grown significantly. A clinical trial showed that HILT was beneficial for slow-healing cesarean sections in diabetic women (81).

However, The development of ideal clinical protocols based on carefully planned, precise clinical research studies is urgently needed. Treatment costs, such as those associated with the purchase and maintenance of PBM equipment, should be weighed against the advantages of reduced care costs and possible improvements in clinical efficacy (82).

5.6. Phage therapy

Bacteriophage (phage) therapy is non-antibiotic antimicrobials to overcome antimicrobial resistance especially multi-drug-resistant (MDR) and extensively drug-resistant (XDR) bacterial infections. Viruses known as phages enter bacteria and multiply, eventually destroying their prokaryotic host (eukaryotic cells do not replicate

phages). Because phages are so highly precise in identifying and infecting bacteria according to the species and frequently the strain level, they are therefore inherently harmless in humans. Phage is considered to be safe to use in clinical treatment. They make up the majority of the human microbiome, which is notable, and is widely distributed throughout our surroundings, including sources of food and water (83).
Phage therapy comes in two types: premade phage cocktails that target one or more species of bacteria known to cover the primary species of bacteria responsible for the infection, similar to empirical antibiotics. or an individualized phage (84).

Phage administration can occur in several ways, including oral, parenteral, or local phage delivery systems. Phage medicines are usually used topically and intravenously one to three times daily for three to seven days, depending on the age and type of wound. The amount of injury determines how much wound preparation is needed. While directly injecting phages into the infection site lessens the likelihood of their loss, this is a more invasive approach. Additionally, topical administration decreases absorption and distribution losses, boosting phages' antimicrobial effectiveness (85).

Preparation Phage therapy was a promising strategy for DFU because it could reduce or eliminate DFU-MDR bacterial infections while providing several advantages over conventional antimicrobial drugs,
Receiving Phage therapy was a potential approach to treating DFU since it offered several benefits over traditional antimicrobial medications and could decrease or eradicate DFU-MDR bacterial infections.
For example, certain phages have enzymes that can break down the biofilms that enable bacteria to withstand drugs. Furthermore, phages can attach to and enter latent bacterial persister cells within a biofilm, where they are prepared to multiply whenever the bacterial cells switch to a replicating state, even though phages cannot replicate in these cells. Certain phages have anti-biofilm properties, which are quite helpful for the treatment of DFIs (84).

Phagetes exhibit a distinctive pharmacological characteristic in that, being biological agents, they "auto-dose" instead of displaying a traditional dose-response curve. Phage replication is significant when bacterial hosts are abundant. However, phage replication stops when there are no more hosts, and the immune system quickly eliminates any phages that are left. Interestingly, there is compelling evidence that some combinations of antibiotics and phages can work in concert, with each agent applying a distinct set of selection pressures to bacteria. (86). Consequently, the bacteria may become more vulnerable to the other as a result of evolving to avoid the first. It is also helpful that phage therapy for DFIs is applied locally since it prevents inadequate perfusion from impeding antibacterial activity. prevents the negative effects of systemic therapy that tends to cause nephrotoxicity since people with DFI may already have compromised kidney function because phages are easily eliminated by the immune system and there is no proof that phage therapy causes nephrotoxicity, even though excretion in urine is possible (87).

Nevertheless, there are certain drawbacks to phages, including a lack of evidence-based guidelines controlling treatment regimens addressing optimal (dosing, frequency, duration, and method of administration) and public hostility to its widespread adoption and operation (83).

6. Conclusion

Advanced treatments for diabetic foot ulcer must undergo thorough evaluation to determine their safety, effectiveness, and cost-efficiency through well-designed, large-scale randomized trials. In conclusion, the conventional ulcer therapy is proven to be highly effective for the majority of cases, and new therapies should be regarded as supplementary treatments for cases where traditional methods are insufficient.

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مبادئ واستراتيجيات جديدة في علاج القدم السكرية

الخلفية: تحدث قرحات القدم السكرية (DFU) في ما يصل إلى 15٪ من جميع مرضى السكري وهي السبب الرئيسي للبتر غير الرضحي في جميع أنحاء العالم. تتطلب قرحات القدم السكرية تحديد السبب وتقييم الأمراض المصاحبة لتوفير النهج العلاجي الصحيح، وهو أمر ضروري للحد من خطر بتر الأطراف السفلية. أدت معدلات فشل العلاج المرتفعة إلى تطوير علاجات جديدة. **الهدف:** تسليط الضوء على الاتجاهات الحالية في إدارة قرحات القدم السكرية التي يمكن أن تحل محل أو تكمل الاستراتيجية الكلاسيكية لإدارة قرحات القدم السكرية، بالإضافة إلى الاستراتيجيات الانتقائية والمستهدفة اللازمة لتحسين عملية الشفاء. **الطريقة:** أجرى المؤلفون، بدقة، بحثًا شاملاً في الأدبيات من خلال استكشاف قواعد بيانات Science Direct و Scopusو PubMedو Web of Scienceبدقة. لقد بحثوا على وجه التحديد عن الدراسات المنشورة والمقالات الأصلية التي ظهرت في المجلات المحكمة المرموقة والتي أفادت بأبحاث أصلية. الاستنتاج: هذه التقنيات الجديدة واعدة ولكنها لا تزال غير مثبتة في الغالب. ينبغي النظر إلى العلاجات الجديدة والأكثر تكلفة بشكل عام على أنها تضيف إلى الأساليب التقليدية وليس بديلاً عنها.

الكلمات المفتاحية: القدم السكرية، تضميد الجروح، عامل النمو، هندسة الأنسجة، تكنولوجيا النانو.