Case Report

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Recent Advances in Approach to Diabetic Foot Ulcer

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Abstract

Diabetic foot ulcers (DFU) develop as a complication of diabetes mellitus and represent significant morbidity, mortality, and healthcare costs. Thorough debridement, wound dressings, offloading, vascular assessment, infection control, glycemic control, and a multidisciplinary approach are needed. Along with this, newer agents such as nanomolecules and nanodrug delivery system are emerging. This overview article discusses recent trends in DFU and its management.

Key Words: Diabetic foot ulcer; DFU; Debridement; Unloading; Nanomolecules; Nanodrug delivery systems.

INTRODUCTION

Diabetic foot ulcers (DFU) develop as a complication of diabetes mellitus and represent significant morbidity, mortality and healthcare costs. It is estimated that 19–34% of patients with diabetes are likely to develop a diabetic foot ulcer during their lifetime, and the International Diabetes Federation reports that 9.1–26.1 million people develop a DFU annually.[1] These numbers are alarming because the clinical consequences are not negligible for the development of DFU. A wide variety of new interventions are being studied to improve wound healing. In this review, we discuss the current standard of care and review current guidelines in DFU. We also review several adjuvants currently in use or being studied to improve DFU outcomes.

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DISCUSSION

Pathophysiology

Diabetic foot ulcers occur as a result of diabetic sensory, motor and autonomic neuropathy. Sensory neuropathy leads to loss of protective sensation; motor neuropathy causes foot deformity and biomechanical abnormalities, while autonomic neuropathy leads to viscoelastic changes in the skin, such as skin dryness. The callus will develop as a result. With repeated microtrauma, bleeding develops under the callus, which can further develop into deep ulcers.

Screening of diabetic ulcer

Annual screening by a clinician or podiatrist for the development of foot sensitivity, peripheral artery disease and skin damage evaluated. (Table 1)

Assessment of wound

Many classification systems prevail for the evaluation of a diabetic ulcer. Many of them consider the degree of ischemia to the last state regardless of

Table 1: Screening and Follow-Up for Diabetic Foot Ulcer Risk and Active Complications of Diabetic Foot Disease, according to IWGDF

Category	Ulcer risk	Characteristics	Follow up frequency
Active pathology	Active	Active ulcer, Charcot arthropathy or infection with or without peripheral artery disease	Rapid referral to specialist/ multidisciplinary team
3	High	In remission: history of diabetic foot ulcer, amputation (minor or major) or end stage renal disease	1-3 mon
2	Moderate	>/= 2 factors among loss of protective sensation, peripheral artery disease and foot deformity	3-6 mon
1	Low	Loss of protective sensation or peripheral artery disease	6-12 mon
0	Very low	No loss of protective sensation or peripheral artery disease	annually

tissue loss or infection. The classification system for leg wounds, ischemia and infection (WIfI) (Table 2) involves grading the degrees of tissue loss, ischemia, and leg infection as none, mild, moderate, or severe.

Table 2: WIfI classification

The Wound, Ischemia, and Foot Infection (WIfI) classification system consists of 3 components graded separately from 0 (none) to 3 (severe).

One component may be dominant but the specific combination of scores is used to estimate the risk of limb amputation at 1 year and the need for or benefit of revascularization.[a]

Wound (W)

Grade	Ulcer	Gangrene
0	None	None
1	Small, shallow	None
2	Deep with exposed bone, joint, or tendon	Limited to digits
3	Extensive, deep, and involving forefoot and/or midfoot with or without calcaneal involvement	Extensive and involving forefoot and/or midfoot Full thickness heel necrosis with or without calcaneal involvement

Ischemia (I)

Grade	Ankle-brachial index Ankle systolic pressure	Toe pressure or transcutaneous oximetry
0	≥0.80 >100 mm Hg	≥60 mm Hg
1	0.60-0.79 70-100 mm Hg	40-59 mm Hg
2	0.40-0.59 50-69 mm Hg	30-39 mm Hg
3	≤0.39 <50 mm Hg	<30 mm Hg

Foot infection (fI)

Grade	Clinical manifestation
0	No symptoms or signs of infection
1	Infection indicated by ≥2 of the following: • Local swelling or induration • Erythema 0.5-2.0 cm around ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous)
2	Infection as described above with: • Erythema >2 cm around ulcer • Involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis) • No signs of systemic inflammatory response (see below)
3	Infection as described above with ≥2 signs of systemic inflammatory response syndrome: • Temperature >38 °C or <36 °C • Heart rate >90/min • Respiratory rate >20/min or $Paco_2$ <32 mm Hg • White blood cell count >12 000/μL or <4000/μL or 10% immature forms

Evaluation of infection must be done by examination for signs of inflammation, active pus discharge, positive wound culture, and elevated ESR. In the case of osteomyelitis, the diagnostic test of choice is bone biopsy and culture. Peripheral arterial circulation in diabetic patients affected by medial calcinosis. Therefore, the toe index is preferred over the ankle index.[2] A toe and arm index of less than 0.70 corresponds to peripheral artery disease.[3] Finger pressure 30 mm Hg or higher, transcutaneous oxygen pressure 25 mm Hg or higher, and skin perfusion pressure 40 mm Hg or higher was associated with a higher rate of ulcer healing.[4] (Table 3)

Table 3: Assessing Ischemia in the Presence of a Diabetic Foot Ulcer

Test	Definition
Palpation of pulses	Palpation of anterior tibial or posterior tibial artery pulsation
Ankle Brachial Index	Ankle pressure compared with arm pressure
Toe systolic blood pressure	Measurement of systolic blood pressure at the toe
Transcutaneous oximetry	Measurement of oxygen tension at the skin surface
Skin perfusion pressure	Measurement of blood pressure required to restore microvascular blood flow afterocclusion

Management

Preventive measures

People in the lowest leg ulcer risk category without loss of protective sensation, peripheral artery disease, or a history of leg complications can undergo annual follow-up with a primary care physician or podiatrist.[5,6] Proper foot care and appropriate footwear.[6] People with two or more risk factors, including loss of protective sensation, peripheral artery disease, and foot deformity, are considered moderate risk and should have a consultation with a footwear specialist (from podiatrist, pedorthist or orthotics) for quality footwear with appropriate fit, which may include pressure-relieving therapeutic footwear.[6] Individuals at moderate risk should return for evaluation by a podiatrist every 3 to 6 months (patients with peripheral artery disease may require evaluation by a vascular specialist Immediate vascular referral is indicated in patients with a diabetic foot ulcer and an ankle pressure less than 50 mm Hg, an ankle-brachial index less than 0.5, a toe pressure less than 30 mm Hg, or a transcutaneous oxygen pressure less than 25 mm Hg.

Debridement

Debridement is a standardized approach used to facilitate healing. Healing is achieved by removal of nonviable wound bed and wound margin tissue, including excess callus at the periphery and nonviable dermal tissue, as well as foreign materials and bacterial components. Although guidelines recommend regular debridement, defined as weekly or every other week, randomized clinical trials are lacking.

Wound dressings

Choose dressings that remove excess fluid to prevent further tissue inflammation and damage from prolonged contact with the wound or wound edge (Table 4). In general, hydrogels are preferred for wounds that produce little exudative drainage, while alginates or hydrofibers are recommended for heavily draining wounds.[7,8]

Table 4: Type of dressings

Dressing type	Characteristics and use
Alginates	These dressings form a damp gel on absorption, necessitating a secondary dressing. They are comfortable, filling dead spaces and managing moderate to heavy exudates effectively. Suitable for wounds with light to moderate serous discharge
Antimicrobial dressings	These dressings contain substances such as silver or iodine that inhibit bacterial growth in the wound, making them suitable for infected wounds or those at high risk of infection. However, it is important to note that, as with each of these categories, there is a lack of strong evidence recommending their use despite their widespread application.
Collagens	Derived from bovine, equine, porcine, or ovine (sheep) sources, these products help stimulate wound healing. Available in various forms such as gel, pad, paste, powder, and sheets. Some dissolve entirely while others need removal per the manufacturer's guidelines. A secondary dressing is usually required. Ideal for wounds showing granulation tissue, as they further stimulate its formation.

Table cont....

Film dressings	Thin, transparent dressings that foster a moist environment, promoting healing and enabling wound assessment without removal. Ideal for superficial wounds with minimal exudate.
Foams	These dressings are capable of absorbing moderate quantities of exudate and can be used under compression.
Gauze	Highly permeable dressing material, suitable for wound cleaning, as a cover dressing, and for securing dressings. Gauze is not generally recommended as a primary wound dressing because it can remove healthy granulation tissue during dry dressing changes.
Hydrocolloids	These bacteria-proof dressings facilitate autolytic debridement. They are not appropriate for infected wounds as they may damage fragile skin. Ideal for wounds with insignificant serous drainage.
Hydrogels	These are glycerin and water-based products available as amorphous gels, sheets, or impregnated dressings. They can be antimicrobial, donate moisture to wounds, assist in autolytic debridement, and possibly reduce pain. They require a secondary dressing and are suitable for low-exudate wounds needing additional moisture.

Off-Loading

Relieving repetitive mechanical stress on the leg by reducing the load on the ulcer is an important aspect of treatment and reduces pressure on the wound by distributing the force over a larger unit area, thereby providing an environment for healing[9] (Table 5). The most effective treatment to relieve the burden of a plantar ulcer on the foot is a non-removable knee-high sensing device, either a total contact cast or a below-the-knee walker that is non-removable. A total contact cast is a special cast shoe applied with minimal padding by a casting technique. A knee walker is a prefabricated boot that is usually applied with Velcro or straps. Both the total contact cast and the walker spread force over a large area and effectively reduce ulcer pressure by up to 80 to 90% compared to a standard shoe.

Table 5: Reducing weight bearing by various offloading measures

offloading methods	Description
Knee-high nonremovable offloading device	total contact cast or knee high walker rendered non removable
Removable knee high and anklehigh walkers	offloading devices that can be removed by patient
Felted foam in appropriately fitting shoes	felted foam applied to atleast ulcer region
Flexor tendon tenotomy	surgical procedure for ulcers on the apex of lesser toes
Achilles tendon lengthening	surgical procedure for plantar forefoot ulcers if nonsurgical treatment fails

Others

Other wound healing techniques include topical fibrin, leukocyte patch, platelet-rich plasma, placental derivatives, sucrose-containing dressings, hyperbaric oxygen therapy, and negative pressure wound therapy (Table 6).

Table 6: Wound healing therapies

Wound healing therapies	Description
Dressing selelction	based on wound characteristics, location, inflammation and amount of exudate
Topical fibrin and leucocyte platelet patch	autologous leucocytes, platelets and fibrin placed on the wound
Placenta derived products	contain growth factors, collagen rich extracellular matrix, and cells that might accelerate wound healing
Sucrose octasulfate dressing	used in treatment of neuroischaemic diabetic foot ulcer
Hyperbaric oxygen therapy	adjunct therapy in neuroischaemicor ischaemic DFU
Topical oxygen therapy	adjunct therapy in DFU when standard of care alone has failed
Negative pressure wound therapy	used in treatment of complicated and postoperative wounds in the diabetic foot

Although many diabetic foot ulcer infections are superficial, some may require surgery to remove the deep soft tissue infection. In the absence of

Treatment of Infected Diabetic Foot Ulcers

Early treatment of diabetic foot infections reduces the risk of hospitalization and amputation.

acute soft tissue infection in forefoot osteomyelitis, antibiotics can be used safely and effectively.

Treatment of peripheral arterial disease

A systematic approach can be used for revascularization based on the assessment of overall operative risk and the anatomical distribution of lower extremity arterial disease. Most patients with chronic limb-threatening ischemia should undergo revascularization. But older age, the presence and severity of medical comorbidities, impaired functional status, and shorter life expectancy are important factors to consider before considering whether revascularization is likely. Primary lower extremity amputation without revascularization may be appropriate in selected patients, including patients who are nonambulatory at baseline and patients with frailty. Both open surgery and endovascular therapy can be appropriate for chronic limb-threatening ischemia.

Nanodrug delivery systems

Nano-drug delivery systems (NDDS) overcome the limitations of conventional DDS due to nano size and application. It is considered a developing process in the field of wound treatment. Recently, several delicately designed nanocarriers have been developed that efficiently load various substances (bioactive and nonbioactive factors) (Table 7-11).

Table 7: Growth factors with nanocarriers

GFs	Carriers	Function	Merits
EGF	PHMB -GelMA hybrid patch	Promote the migration and proliferation of multiple types of cells (keratinocytes, fibroblasts and endothelial cells) and enhance angiogenesis	Good biostability
EGF	Chitosan nanoparticles	Induce thorough reepithelization, sufficient collagen deposition and accelerated collagen maturation	Good biocompatibility
bFGF	Decellular dermal matrix	Enhance granulation tissue formatting, angiogenesis and collagen deposition	Good endothelial inducibility
rhEGF	Nanofibre scaffolds	Induce faster wound healing activity in dorsal wound	Electrospinning fibres; prolonged releasee of GFs
EGF	Chitosan/PVA heterocomposite hydrogel	Reduce inflammatory response , faster collagen deposition and advanced collagen maturation	Release EGF and PHMB in ion rich environment
PDGF-BB	Nanohydrogel	Destruct biofim	Destruct the biofilm, keep stable structure at room temperature
rhEGF	Sodium hydroxymethyl chitosan nanoparticles	Exhibit more stability against proteolysis and preserve biological activity	Increasing GFs proteolytic resistance

Table 8: Delivery of Genes/Proteins/Peptides with Nanocarriers for Diabetic Wound Healing

Cargos	Carriers
MicroRNA mR31-5p	Milk derived exosomes
KeapI siRNA	Lipoproteoplex nanoparticle
MMP-9 siRNA	Hyperbranched cationic polysaccharide derivatives,hydrogel based on
si RNA -29a gene	HA-PEI nanoparticles
siRNA (downregulation of PHD)	Gold nanoparticles
Dicer substrate small interfering RNA (DsiRNA)	Gold nanoparticle

Table 9: Stem Cell/Exosomes Loading Nanomaterial for Diabetic Wounds

Stem sells	Delivery systems
BMSCs	Nanofibrescaffold, human epidermal growth factor-curcumin bandage biconjugate
ADSCs	Injectable hydrogels
Gingival mesenchymal stem cells	Chitosan/ silk hydrogel sponge
hFDSPC	HA
Mesenchymal stem cell	ADM-RGO composite scaffolds

Table 10: Delivery of Drugs for Efficient Diabetic Wound Healing

Drugs	Carriers
curcumin	Injectable hydrogels,chitosan based hydrogel,gelatin microspheres
Insulin	pH and glucose dual-responsive injectable hydrogels PLGA nanofibrous scaffolds
quercetin	Topical Hydrogel system
Dimethyoxal glycine	Porous electospun fibrous membrane
Hyaluronine oligosaccharide	pH responsive calcium alginatehydrogel

Table 11: Delivering Oxygen/NO for Diabetic Wound Treatment

Material	Carrier
Oxygen	microspheres
Calcium peroxide	oxoBand
Sodium percarbonate	Plycaprolactone based nanofibres
QCN oxygen	nanoemulsion
Perfluorocarbon emulsions	Chitosan nanoparticles
MnO2	Dex-SA-AEMA hydrogel

1. Bioactive molecules: growth factors, genes/proteins/peptides, stem cells/ exosomes, drugs
2. Non-bioactive substances: metal ions, oxygen

NDDS refer to drug delivery systems with nanoscale particle diameters that have the property of improving drug stability, sustained release, and controlled drug release and can be made of a variety of biomaterials. (Fig. 1) There have been an unprecedented number of NDDS-loaded therapeutic agents used in the treatment of diabetic wounds.

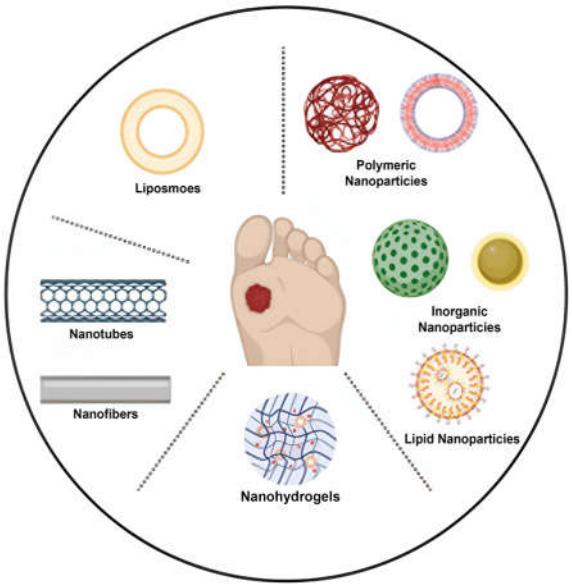

Fig. 1: Drug delivery systems

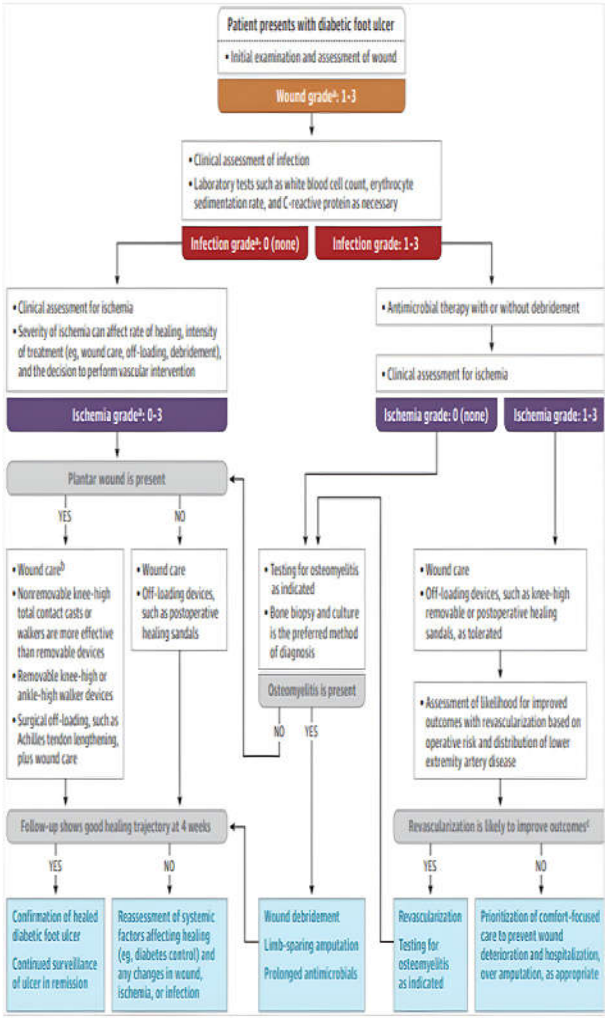

Fig. 2: Algorithm for active diabetic foot management

Long term management and follow up

In these patients, long-term follow-up is necessary, complications can occur when they are left unattended, as well as for better rehabilitation (Table 12).

Table 12: Multidisciplinary approach of long term management

Parts	Description
Multidisciplinary team approach	Structured service including medical, podiatry, infectious disease, vascular surgery, primary care
Therapeutic footwear	Prescription and management of footwear
Rehabilitation, psychological care and nutrition	Mental health, nutritional deficit and overall quality of life
Healing rate	Healing rates of diabetic foot ulcers
Recurrence rate	Recurrence rate of DFU after healing

CONCLUSION

The treatment of non-healing diabetic wounds faces many difficulties. The complex pathological process of diabetic wound healing and the various conditions of diabetic patients constitute obstacles to current treatment outcomes. Sharp debridement, wound dressings, offloading, vascular assessment, infection control, glycemic control, and a multidisciplinary approach are needed. Many therapeutic agents (GF, genes, stem cells, drugs, metal ions and oxygen) related to healing stages and mechanisms have been studied to establish the equilibrium level of a key mediator for better wound healing and various nanodrug delivery systems (liposomes, NPs). , nanofibers and nanohydrogel) have been created for the treatment of diabetic non-healing wounds.

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