

Diabetic foot ulcers: Contemporary assessment and management

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Abstract

Diabetic foot ulcer disease is the combination of vasculopathy, neuropathy and infection. It is important to identify the main aetiology and to treat it for optimal ulcer healing so that limb amputation may be prevented. A literature review spanning five years (2017-2021) was performed to assess the current understanding of these aetiologies and management options for their treatment. Peripheral artery disease is prevalent in patients with diabetes. Before performing any amputations, whether minor or major, vascular supply in these patients needs to be evaluated and, if needed, improved. Diabetic neuropathy is a long-term complication of uncontrolled diabetes. Patients' education is very important with respect to selfcare and prevention of foot complications arising out of minor trauma in diabetic population. Better foot care and regular use of off-loading shoe wear can prevent neuropathic diabetic foot ulcers. Infection in diabetic patients is mostly polymicrobial and it can present as superficial or deep infections. Early diagnosis, use of broad-spectrum antibiotics, and aggressive debridement, when needed, is advocated to prevent foot amputation. Contemporary treatment armamentarium provides many options for treating diabetic foot ulcers. Nevertheless, one must exhaust all preventive strategies to avoid ulcers in the first place. Once an ulcer has developed, it should be managed aggressively with appropriate soft tissue and, if required, with bony procedures. The current narrative review was planned to explore the current understanding about the main aetiologies of diabetic foot ulcers and about the available treatment options.

Keywords: Diabetic foot, Peripheral artery disease, Neuropathic ulcer, Ischaemic ulcer.

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Introduction

Diabetic foot ulcers (DFUs) are a common complication of diabetes with a prevalence in the general diabetic population of 4-10% and there is a lifetime risk ranging 19-34%.¹ Diabetic foot is a major public health problem as

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Figure-1: Healing ulcer with neuro-infected ischaemia.

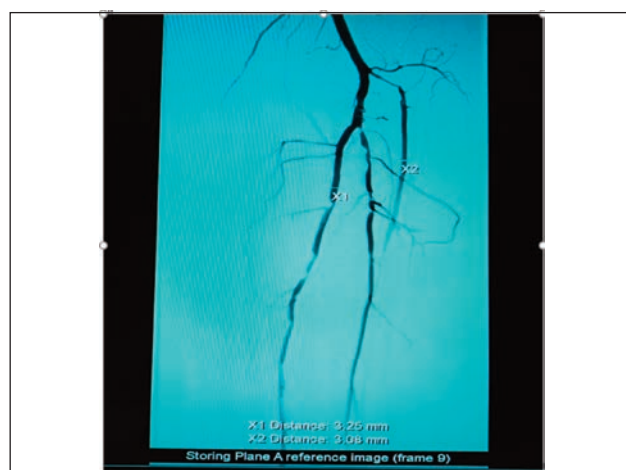


Figure-2: Angiogram showing infra-popliteal occlusive disease in diabetic patients.

15% of diabetics develop a foot ulcer over the life span, and 85% of the amputations are preceded by a non-healing foot ulcer.² Among all possible complications of diabetes mellitus (DM), diabetic foot problems are the leading cause of hospitalisation.³ Diabetics have a 15-30 times more risk of amputation compared to non-diabetics. A combination of neuropathy, infection and vasculopathy causes DFUs, (Figures 1-2). According to epidemiological data, 50% DFUs are due to neuropathy, 15% are due to peripheral artery disease (PAD), and the other 15% are due to both neuropathy and PAD. DFUs are associated with a high recurrence rate after the first ulcer healing. Risk factors for DFUs include a history of limb amputation.⁴ Along with somatic neuropathy and PAD, this population is also prone to cardiac autonomic neuropathy, coronary artery disease

(CAD), diabetic nephropathy (with or without renal failure), and cardiac nephropathy.⁵ All individuals with a significant renal impairment should ideally be assessed by a renal physician prior to any procedures. Furthermore, due to the substantial mortality risk of lactic acidosis, metformin must be discontinued 48 hours before elective angiography.⁶ CAD and cardiac autonomic neuropathy (CAN) raise the risk of perioperative cardiac events.

DFU aetiologies

Approximately 50% DFUs occur on the plantar aspect of the foot.⁷ It is important to evaluate the aetiology of DFU, as a correction of the aetiology will heal the ulcer. The risk factors for the development of DFUs include inadequate glycaemic management, peripheral neuropathy, PAD and immunosuppression. Motor, autonomic and sensory neuropathy are caused by the complicated production of advance glycation end products and cytokines that are brought on by persistent hyperglycaemia.² Further callus formation can result from skin sensitivities induced by autonomic changes, making sweat glands less efficient. DFU aetiology can readily be identified by ulcer location and its associated clinical findings. The neuropathic ulcers are painless and deep. They have punched-out edges present at pressure points. Peripheral pulses are mostly palpable in these patients. Common sites for these ulcers are at the heel or at the head of the metatarsals. Ischaemic ulcers mostly present at the tip of the toes, or along the dorsum of the foot and the shin. They are painful and have little granulation tissue. Dorsalis pedis and posterior tibial pulses are not palpable.⁸ Patients can present with ulcers of combined aetiologies, such as neuro-infective or neuro-ischaemia. Infection develops in the background of ischaemia/neuropathy, (Figure 1).

The standard of care for DFUs include off-loading, sharp debridement and wound moisture balance along with infection control and PAD management. A variety of advance modalities that target the distinct pathophysiological aspect of impaired wound healing in diabetes are being studied as adjunct therapies for non-healing ulcers. These modalities include growth factors, stem cells, cultured fibroblasts and keratinocytes, bioengineered skin substitutes, acellular bioproducts, human amniotic membranes, oxygen therapy, negative pressure wound therapy and energy therapies. Additionally, the use of advanced biomaterials and gene delivery system is being investigated as a method of effective delivery of substances to the wound bed.⁹ Lazzarini et al. published an acronym (MADADORE) to assist clinicians to remember the recommended DFU management principles.¹⁰ This includes Metabolic/Medication, Assessment, Debridement, Antibiotics,

Dressing, Offloading, Referral and Education. A systemic review has shown that initiation of multidisciplinary team care model results in a reduction in major amputations in 94% (31 of 33) studies.¹¹

Treating ischaemic ulcers

PAD is more prevalent in diabetics than in the general population. It typically involves distal superficial femoral and infra-popliteal arteries.¹² The atherosclerotic segments are calcified, diffuse, and involve all the three tibial vessels. Neuropathy masks the symptoms of ischaemia as most patients do not have classic presentations of intermittent claudication and rest pain.¹³ The very first presentation in these patients can be with an ischaemic ulcer or toe gangrene. It is important to evaluate these patients to improve the blood supply to the foot before performing any form of minor or major amputation. In an intact foot without ulcer or gangrene, the diseased axial artery and collaterals are adequate to provide blood, but they become inadequate in case of an active ulcer. A non-healing ulcer needs many times more of the baseline blood supply to achieve healing.

Ankle-brachial pressure index (ABPI) is a useful bedside tool for diagnosing and assessing PAD severity in diabetics.⁸ Its ratio of the peak systolic pressure measured at the ankle arteries to that found in the brachial arteries 0.91-1.30 denotes normal; 0.4-0.89 represents mild to moderate occlusion; and 0.4 represents severe occlusion. If the ratio is <0.9, the ulcer is ischaemic and has a low probability of healing until the vascularity is improved. Value >1.3 signifies highly calcified arteries that are not adequately compressible.

One of the main disadvantages of the ABPI is that it is erroneously elevated especially in patients with long-standing DM. In those situations, toe-brachial pressure and other non-invasive tests can detect PAD. Transcutaneous oxygen pressure (TcPO₂) assessment is a non-invasive method for quantifying skin oxygen. This is especially helpful in advanced disease of lower limb arteriopathy for assessing cutaneous ischaemia. It is a determinant of spontaneous healing when pressure is >30mmHg and a disadvantageous course when the pressure is <10 mmHg.¹⁴

Ultrasound is a useful investigation to document the severity of PAD in these patients which is cost-effective, reproducible and is free from ionizing radiations. It can provide useful information about the diseased segments but is limited in evaluating infra-popliteal vessels surrounded by tibia and fibula bones.

Computed tomography angiography (CTA) is a non-invasive method for evaluating PAD. The use of contrast

media is a limitation which can be nephrotoxic, especially in patients with compromised renal functions. It also uses ionising radiation. On CTA, it is difficult to differentiate contrast from calcification. PAD is more dominant in infra-popliteal arteries in diabetics where it is difficult to comment on CTA for tibial occlusive disease, but CTA is a useful investigation to rule out proximal occlusive disease.

Magnetic resonance angiography (MRA) is another non-invasive investigation for evaluating these patients whose information is not limited due to calcification. Gadolinium used as contrast in magnetic resonance imaging (MRI) can cause nephrogenic fibrosis.¹⁵⁻¹⁹ MRI does not use radiation. This can be a useful non-invasive investigation in evaluating PAD in these patients. But it needs cooperative patients and is contraindicated in claustrophobic patients who cannot lie still for longer durations.⁸ Moreover, this cannot be used in patients with metallic implants and stents. Lower leg catheter angiography, although invasive, is the gold standard for evaluating infra-popliteal vessels. Its images are not hindered by calcifications, (Figure 2). This can also be used both as a diagnostic and therapeutic investigation. Contrast-induced nephropathy can be one of its limitations in patients with underlying diabetic nephropathy. In those high-risk patients, carbon dioxide (CO₂) angiography can be used.

Both surgical and endovascular methods are effective in improving the blood supply of the ischaemic ulcer.²⁰ Neovascularisation enhances blood flow to the ulcerated area as well as to the deep tissue surrounding it. Increased microcirculation is critical for ulcer healing. Infra-inguinal bypasses using veins have excellent limb salvage rate with minimal perioperative morbidity and mortality.²¹ These are best served for patients with good life expectancy and who carry low anaesthesia. Any pedal artery can be used as the outflow. The principle is to maintain an inline flow to the foot to help the wound heal or the pain to settle. An adequate -size vein of at least 3 mm, without fibrosis and stenosis is preferred for the success of these procedures. This can be identified and mapped preoperatively. The vein can be used either in reversed, non-reversed or in-situ fashion. Performing anastomosis in severe calcified arteries may be challenging as they are not compressible and operative field may not be dry. This issue is sorted by innovatively using thigh tourniquets, intraluminal balloons, and glues to achieve a relative bloodless operative field. Many studies from the developed world have shown effectiveness of these bypasses ad limb salvage rate. In low- and middle-income countries (LMICs), there are limited centres that may reproduce these results.²¹ It is very important to discuss locoregional results with patients while making a treatment decision.

Infra-inguinal bypass is a major surgery that may not be ideal for patients who have multiple comorbidities, which is often the case with DFU patients, or in patients who do not have suitable veins. In such cases, endovascular therapy is an alternative which is minimally invasive and can be performed under local anaesthesia. This modality has rapidly evolved as most interventionists opt for 'endovascular-first approach' in most cases.⁸ Endovascular techniques currently available are percutaneous transluminal angioplasty (PTA) with and without stenting, subintimal angioplasty, PTA with drug-coated balloons, covered stents, cryotherapy, brachytherapy and atherectomy devices. Drug-eluted balloons and stents prevent neointimal hyperplasia and decrease the risk of re-occlusion.⁸ Sirolimus-eluting stents have been shown to inhibit neointimal hyperplasia in the coronary vasculature, and there is also data about their effectiveness in femoro-popliteal and infra-popliteal vessels.²² Subintimal angioplasty helps in improving blood flow in occluded arteries that are not crossable by the conventional intraluminal route by guidewire by standard technique. This helps in achieving luminal patency in the occluded arteries. The atherosclerotic calcified segments in diabetics are very stiff, making simple angioplasty ineffective. Atherectomy devices can debulk these lesions to facilitate angioplasty and saves the arteries from stent placement. This is advantageous as re-stenosis due to in-stent stenosis is more difficult to treat than simple re-stenosis.

The techniques to cross the difficult lesions have also improved. As discussed, in case of failure of the 'antegrade' intraluminal approach, the subintimal approach is the option. Even if it fails, the 'retrograde' trans-pedal arteries approach can be used to cross these lesions. Subintimal arterial flossing with antegrade-retrograde intervention (SAFARI) is a novel technique to cross these difficult lesions.^{23,24}

The reported limb salvage rate following either surgical, endovascular or hybrid revascularization techniques is 80-85%.²⁵

Diabetic neuropathy

About 50% DM patients develop peripheral neuropathy within 25 years of disease onset. Neuropathy of distal lower extremities is subdivided into sensory, motor and autonomic neuropathies.²⁶ The combination of sensory and motor peripheral neuropathy leads to unequal foot load accompanied by insecure gait. Diabetic neuro-osteoarthropathy (DNOAP), or Charcot's foot, is characterised by the sterile destruction of bones and joints.³ Due to neuropathy, the process proceeds painlessly. Visual inspection shows typical reactive hyperemia in line



Figure-3: Multiple non-healing neuropathic leg ulcers.

with swelling and destruction of osseous structures with sintering of the metatarsus region.³ Patients can present with neuropathic ulcers, (Figure 3).

Off-loading

High plantar pressure has been recognised as a risk factor for ulcer formation, and effective off-loading is considered the mainstay of its treatment. Off-loading is a crucial aspect of treatment and aims at redistributing pressure away from the ulcer site, thereby reducing further tissue trauma and facilitating the wound healing process.²⁷ This can be achieved via an offloading device, such as a total contact cast (TCC) or controlled ankle motion (CAM) walker.²⁸ Pressure redistribution has been linked to positive outcomes. Resection of bony protrusions from a chronic ulcer lesion aids in pressure reduction. Following that, primary closure of the surgical wound becomes one of the most key goals in achieving healing.

Treating diabetic foot infections

Diabetic foot infection is divided into superficial and deep types. Superficial infection is localised without systemic involvement and is treatable with antibiotics.²⁹ Spreading infection or that with sepsis needs debridement. The principle of debridement is to remove all the necrotic and infected tissues. Cultures are taken from deep wounds and antibiotics are adjusted accordingly. There is level 1 evidence that effective communication about the degree of foot infection among the medical community is more objective. This helps better in the documentation and assessment of the therapeutic response and treatment improvement. The Site-Ischaemia-Neuropathy-Bacterial Infection-Area-Depth (SINBAD) score is one such tool that helps to prognosticate the disease (Table 1).³⁰

The infection in a diabetic is polymicrobial. It spreads in the

Table-1: Site-Ischaemia-Neuropathy-Bacterial Infection-Area-Depth (SINBAD) score.

Category	Definition	Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischaemia	Palpable blood flow intact: At least one palpable pulse	0
	Clinical evidence of reduced pedal flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial Infection	None	0
	Present	1
Area	Ulcer < 1 cm ²	0
	Ulcer ≥ 1cm ²	1
Depth	Ulcer confined to the skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon, or deeper	1
Total possible score		6

bloodless tract along the tendon sheaths towards the calf.³¹ One of the main reasons why DFUs are so difficult to heal is related to the presence of biofilms that promote wound inflammation and there is remarkable lack of response to host defences / treatment options, which can lead to disease progression and chronicity.³² Patients and even clinicians ignore the severity of infection until the patient has advanced disease and has developed osteomyelitis. The most common pathogens in DFU infections are gram-positive cocci; mainly *staphylococcus (S.) aureus* and *S. epidermidis*. The most common gram-negative pathogens are *Escherichia (E.) coli*, *Klebsiella (K.) pneumonia*, *Proteus species* and *Pseudomonas (P.) aeruginosa*.³³ Anaerobic pathogens are more commonly isolated in necrotic wounds and infections of ischaemic feet.³⁴ Antibiotic regimens are usually selected empirically at first, then modified, if required, based on the results of culture and sensitivity tests, as well as the therapeutic outcome of the patient. Treatment strategy, especially in serious cases, may need to be broad-spectrum, but definitive therapy, especially in serious infections, may often be more targeted.³⁵ Osteomyelitis, a serious complication of DFU infection, increases the risk of treatment failure and increases the amputation risk. Osteomyelitis is suspected when an ulcer lies over a bony prominence, especially when it fails to heal despite adequate off-loading.³⁶

Common pitfalls in managing diabetic foot infections

1. Missing patients with necrotising fasciitis (NF): The classic features of NF are not present in these immune-compromised patients. A high index of suspicion is needed to pick these cases. The suspected patients should be hospitalised, resuscitated and offered early aggressive treatment to salvage the limb.
2. Not starting appropriate and broad-spectrum antibiotics early: As the infection is polymicrobial and these are immune-compromised patients, it is better to start broad-spectrum intravenous antibiotics covering

Table-2: Perfusion, Extent, Depth, Infection and Sensation (PEDIS) score to grade severity of infection.³⁷

Clinical Manifestations	Infection Severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥ 2 manifestations of inflammation (purulence, erythema, tenderness, warmth, or induration), but any cellulitis /erythema extends ≤ 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness.	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥ 1 of the following characteristics; cellulitis extending > 2 cm lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone.	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, acidosis, severe hypoglycemia, or azotemia)	Severe	4

gram-positive, gram- negative and anaerobes. Culture obtained from superficial wounds may not represent actual pathogens. Deep and multiple cultures should be obtained for antibiotic selection.

3. Consider antifungal medications in these patients as most patients have fungal infections associated with a bacterial infection. Fungal infections should be checked especially in patient who are not responding to the antibiotics.

Perfusion, Extent, Depth, Infection and Sensation (PEDIS) score is an objective way to characterise mild, moderate and severe infections (Table 2).³⁷

Antibiotics are most effective when the necrotic and septic focus is minimal. Early and aggressive debridement makes a difference. Too much relying on conservative treatment is not advisable, especially in patients with deep infection.

4. Good glycaemic control helps to control infection better.
5. Ulcers, abscesses, wet or dry gangrene, and NF require surgery to prevent systemic sepsis. Patients are usually in denial due to lack of pain and therefore seek medical attention late which allows the infection to aggravate, leading to multiple bacteria, including anaerobes. These patients will develop sepsis if they wait too long and present with right shift neutrophilia and increased blood glucose levels due to immunosuppression and PAD. Plain roentgenograms may reveal gas in the tissue. In these instances, aggressive debridement is required with the opening of facial planes where the infection may have spread. If the infection has led to

osteomyelitis, one may need to consider digital amputations or forefoot amputation to limit infection and for limb salvage. In early bone involvement, one can consider antibiotic-impregnated bone beads to control the infection and promote granulation tissue.³⁸

6. For definitive wound closure, one needs to ensure healthy underlying tissue free of infection. The patient needs to be optimised with controlled glycaemia and negative markers for systemic sepsis. Local flaps would depend on the available blood supply where the perforators would need to be confirmed with sonography. With large tissue defects, free flaps may be required.³⁹

Bone pathology leading to infection

DFUs are one of the most prominent and distressing symptoms of diabetes. An estimated 15% of diabetic patients will develop a foot ulcer within their lifetime.⁴⁰ This complication has long been recognised as a major health concern, resulting in numerous emergency department visits, hospitalisations, and, sadly, a high rate of amputations and premature deaths.⁴¹ More than half of diabetic individuals with DFUs get infected, with 20-30% of affected limbs necessitating amputations. Moreover, diabetic patients with DFUs have a 2.5-fold greater risk of death when compared to diabetic patients without DFUs.⁴² Chronic foot ulcers are the precursors to amputation in 80% of cases. Prominent bone in the presence of peripheral neuropathy acts as a nidus to initiate ulcer, particularly on the plantar aspect and is also associated with a high rate of recurrence. The reason for prominent bone could be native anatomy or abnormality secondary to malunited fractures, previous dislocation, or bony changes following partial foot amputations. In diabetic patients, motor neuropathy leads to intrinsic minus foot, resulting in toe contractures.⁴³ Surgical options include partial or complete ostectomy, osteotomy, or fusion. Generally, in the presence of osteomyelitis, one should consider excising the bone.

Osteotomy

DFUs are usually treated with conservative management based on debridement, topical agents, and nonsurgical off-loading. However, the recurrence rate following such standard care is reported to be high.³ In the case of recurrent ulcers, a surgical off-loading technique, such as the metatarsal osteotomy (MO), is indicated. Osteotomies aiming at dorsally translating the metatarsal head to treat DFUs showed very promising results in terms of healing rate and time to heal when compared with conservative standard management. Additionally, complications, such

as rates of ulcer recurrence, ulcer transfer, infection and non-union, seem to be less than those reported following standard care. Based on these findings, surgical off-loading via metatarsal osteotomies should be considered as the first-line treatment for complicated DFUs, and some non-complicated wounds as well, mainly those with healing delay.⁴⁴ Diaphyseal osteotomies are also considered safe and effective method for treating DFUs. Minimally invasive distal metatarsal diaphyseal osteotomies (DMDO) are safe and effective method in promoting chronic plantar DFU healing, regardless of the grade of severity, by the reduction of the high plantar pressure under the metatarsal heads.⁴⁵ Removal of bone helps in decompressing the pressure point. From a conceptual perspective, this is simple, but requires a lot of forwarding planning, because if this is done in isolation, it may sometimes lead to instability. If instability is anticipated and there is no osteomyelitis, one should contemplate realignment osteotomy and fusion.

Corrective osteotomies

Surgical bone reconstructive procedures of the foot and ankle in diabetic patients must be considered when performing evaluation of a diabetic foot for patients with pre-ulcerative lesions and pre-existing wounds.⁴⁶ Osteotomies are important to realign bone to reduce pressure on soft tissues. These procedures need internal or external stabilisation. MOs are frequently performed for decompression as first MO or midfoot osteotomies in Charcot deformities to realign the hindfoot with the midfoot.⁴⁷⁻⁴⁹ MOs preferably should be done distally as proximal osteotomies can lead to ulcers due to the high forces during push-off.

Joint deformities also predispose to ulcers. For example, Hallux rigidus leads to ulcers and a restricted range of motion (ROM). In such a situation, cheilectomy addresses both issues in terms of reducing pressure, allowing the ulcer to heal and simultaneously improving the joint ROM.

Arthrodesis

Arthrodesis are good options for managing patients with diabetic foot who require digital deformity correction to achieve digital ulcer healing or management of diabetic foot infection.⁵⁰ Malaligned joints because of previous trauma may be the precursors of ulcers. These joints could be rigid or flexible. To reduce the pressure causing the ulcer, realignment and stability of the joint with fusion is required for limb salvage. Usually, external fixation options including casts are preferred rather than internal fixation in areas of potential infection. Arthrodesis is regarded as an option for the treatment of Charcot arthropathy in the coalescence and reconstruction phases only.⁵¹ The current belief is that

an operation done during the acute, developmental stage will result in inadequate internal fixation because of fragmentation of bone and may contribute directly to destruction of the joint architecture.

A multidisciplinary approach involving endocrinologist as well as vascular and orthopaedic surgeons helps in preventing further spread of the disease and providing options that keep the patient mobile with appropriate measures, including prosthetics, where required. These multidisciplinary strategies decrease the number of amputations and return the patient as an independent productive member of society. Arthrodesis has demonstrated the potential for early operative treatment to restore anatomical alignment and improve the functionality of diabetic patients with stage-I Charcot arthropathy.⁵²

Preventive aspects

Promoting the accessibility of podiatry services within the community as well as reviewing patients' risk of diabetic foot problems or those in need of amputation on a regular basis is what is needed. NICE recommends annual diabetic foot assessments in primary care or podiatry clinics to enable early detection of debilitating diabetic foot complications.⁵³

Conclusion

Contemporary treatment armamentarium provides many options for treating DFUs. Nevertheless, one must exhaust all the preventive strategies to avoid ulcers in the first place. Once an ulcer has developed, it should be managed aggressively with appropriate soft tissue and, if required, bony procedures.

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