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UPDATE ARTICLE

Management of Diabetic Foot

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Abstract: ***The diabetic foot is a major medical, social, and economic problem not only in developing countries like India, but also in developed countries. Even in most developed countries, the annual incidence of foot ulceration among people with diabetes is about 2%. It has been estimated that every 20 seconds a lower limb is amputated due to complications of diabetes. Mortality following amputation increases with level of amputation and ranges from 50% to 68% at 5 years, which is comparable or worse than for most malignancies. Recognizing the importance of starting treatment early may allow practitioners to prevent progression to severe and limb-threatening infection and potentially halt the inevitable pathway to amputation. This article reviews the various modalities available in the assessment and treatment of diabetic foot.***

Introduction

With 65 million diabetic patients and 130 million feet to be taken care of, India is a country where 1,00,000 lower extremity amputations occur per year.[1–3] According to experts, even though this is still a grossly underestimated figure, the horrifying figures recommend an urgent reality check not just on the part of awareness about the newer treatments modalities in the area of diabetic foot management for the Indian doctors but also an increased awareness among the masses.

Worldwide, more than a million lower leg amputations are performed each year as a consequence of diabetes.[4] *Each year 4 million people get a new diabetic foot ulcer.* Foot ulcers precipitate about 85% of diabetic amputations.[5] Key epidemiologic points about diabetic foot ulcer can be summarized by the "Rule of 15":

- 15% of diabetes patients will experience a foot ulcer during their lifetime.
- 15% of these foot ulcers will progress to osteomyelitis.

Even with optimal multidisciplinary care, 15% of diabetic foot ulcers will result in a lower extremity amputation at some level.

The principal causes of diabetic feet are neuropathy, ischemia, infection, limited joint mobility (LJM)/foot deformities, and altered/increased plantar pressure. Neuropathy is the major component of nearly all diabetic foot ulcerations.

Charcot's Foot

Another complication that is associated with diabetic neuropathy can be the development of Charcot's foot (CF). Approximately 1% of people with diabetes suffer from CF.[6] It is a progressive condition whereby the foot is prone to spontaneous fracture with little or no trauma, joint subluxation, and severe, debilitating foot deformity.[7]

Charcot is the most challenging complication of diabetic foot. It is a potentially disabling condition affecting the foot and ankle. Early symptoms are mild swelling, redness, and localized increased skin temperature of foot and ankle in a setting of diabetic peripheral neuropathy (DPN). Sometimes the foot suddenly and unexpectedly collapses with fractures, dislocations, and ulceration. Even history of major trauma is not there. High index of clinical suspicion is the key in diagnosis and management of CF.

Generally it is common in patients between 50 and 60 years of age, with long duration of diabetes having sensory-motor autonomic neuropathy, bounding pedal pulses. Acute CF should be differentiated with cellulitis, acute gouty arthritis, thrombophlebitis (DVT), and osteomyelitis. X-ray of the foot may initially appear normal so MRI of the foot is the investigation of choice in patients with suspicion of having CF. Sometimes sequential radiography at 2-week interval is useful in diagnosis.

Early diagnosis of Charcot's joint is crucial with immediate rest, immobilization, and offloading until diagnosis of CF is ruled out.

Neurological Assessment

Sensory Neuropathy

The simplest way of assessing sensory neuropathy is by Semmes–Weinstein (SW) monofilament (10 g); four or more absent sites is an indicator of neuropathy.

Biothesiometry is for diagnosis and to quantify and follow up of DN.

- Low risk – vibration perception threshold (VPT) < 15V
- Intermediate risk – VPT 16 – 24V
- High risk – VPT > 25V

Neuropad

It is the simplest method to detect autonomic neuropathy. It is a simple visual indicator test which uses a color change to define the integrity of skin sympathetic cholinergic innervation.[8]

Corneal Confocal Microscopy

The early neuropathy assessment (ENA) team is a group of clinician-scientists led by Professor Rayaz A. Malik, based in the Centre for Endocrinology and Diabetes, Institute of Human Development. The ENA team has pioneered the use of *in vivo* corneal confocal microscopy (CCM) as a rapid, noninvasive ophthalmic instrument to monitor damage and repair of corneal (sub-basal) nerves as a surrogate endpoint of diabetic and other peripheral neuropathies in real time. The team also has developed ACCMetrics, a fully automated image analysis software, for the Heidelberg HRTIII confocal microscope allowing rapid and objective quantification of corneal nerve fiber morphology.[9]

Motor Neuropathy

Plantar pressure is the most important aspect to be addressed. Pressure is the critical quantum that determines the extent of harm done to the foot both while standing as well as walking.

Foot Pressure Studies in Diabetic Neuropathy

Semi-quantitative assessment can be done using Pressure stat or Harris mat and quantitative assessment is done using foot scan, in-shoe technique, bare foot technique.

Clinical Evaluation of Peripheral Vascular Disease

Symptoms

Symptoms include intermittent claudication, nocturnal pain, rest pain, cold feet, non-healing wound, and wound that requires repeated debridement.

Palpation of Pulses

Palpation of peripheral pulses including the femoral, popliteal, and pedal vessels (dorsalis pedis and posterior tibial) should be part of the regular physical examination.

Ankle/Brachial Index (ABI)

Simple to perform, the ABI measures the patency of lower extremity arterial system using a handheld Doppler probe and blood pressure cuffs. The ABI is calculated as a ratio of systolic blood pressure measured in the posterior tibial and dorsalis pedis arteries of the ankle, taking the highest of the two, divided by the systolic blood pressure in the brachial artery measured in the arm. Low ABI ratios are associated with high vascular risk[10] (Table 1).

Toe pressure and toe/brachial index

Toe pressure is normally approximately 30 mmHg less than ankle pressure. An abnormal TBI is <0.70.

Pulse Volume Recording (PVR)

The PVR technique is useful as an initial diagnostic test for patients with suspected lower extremity peripheral arterial disease (PAD) and to assess limb perfusion after revascularization procedures, and it can predict risk of critical limb ischemia and amputation.[11]

Transcutaneous Oxygen Tension

Transcutaneous oxygen tension ($TcPO_2$) is a noninvasive method to measure tissue perfusion. It reflects very well the metabolic state of lower limbs. $TcPO_2$ is currently used in clinical practice in the management of the vascular diabetic foot in particular, it is important in determining amputation level, wound healing evaluation, and revascularization procedures. $TcPO_2$ is not affected by arterial calcification and is particularly useful in evaluating PAD in diabetic patients;

Table 1 | Ankle / Brachial Index Interpretation

>0.9 Normal
0.7 to <0.9 Minimal disease
0.5 to <0.69 Moderate disease
<0.5 Critical stenosis

in addition, it has a good reproducibility. Nevertheless, there is not thus far a universally recognized specific cutoff of $TcPO_2$ for the diagnosis of PAD.[12]

Skin Perfusion Pressure

Skin perfusion pressure (SPP) is the blood pressure at the capillary level in the skin. Normal SPP is greater than 50 mmHg. SPP measurement from 30 to 50 mmHg is diagnostic for PAD or microvascular disease and a reading of less than 30 mmHg denotes severe vasculopathy. Obtaining SPP can help predict diabetic wound healing. If SPP is greater than 40 mmHg, there is a high probability for wound healing. If it is 30 mmHg, there is only an 85% chance of healing. If it is 25 mmHg, the probability of healing drops to nearly 50%.[13]

Handheld Infrared Thermometer

It is considered as the glucometer of the foot – affected foot temperature is at least 2°C higher than the contralateral foot.

Imaging the Diabetic Foot

Plain radiograph film is an important initial assessment tool for evaluating infection, foreign bodies, and deformity. Radiographs of the affected foot are a must and represent the gold standard.[14]

Other imaging studies include CT scan, MRI scan, nuclear medicine studies, ARANZ camera (advanced three-dimensional silhouette camera) (ARANZ Medical, New Zealand). It gives an exact measurement of the wound. Hyperspectral Imaging (OxyVu, HyperMed, Inc., MA, USA) can detect changes in the diabetic foot and help predict and understand ulceration mechanisms.

Majority of diabetic foot lesions in India are neuropathic infective. For the management of diabetic foot ulceration (DFU), classification is required for auditing of diabetic foot care. Wagners (Table 2) and University of Texas (Table 3) are the two classification systems commonly used to classify DFU.

Table 2 | Foot Ulcer Classification: Wagner System (modified) most commonly used

Grade	Lesion
0 A B	No open lesions; ± deformity, cellulites A=Ischemic B=Infected
1 A B	Superficial ulcer Ischemic Infected
2 A B	Deep ulcer to tendon, or joint capsule Ischemic Infected
3 A B	Deep ulcer with abscess, osteomyelitis, or joint sepsis Ischemic Infected
4 A B	Localized gangrene-forefoot or heel Ischemic Infected
5 A B	Gangrene of entire foot Ischemic Infected

A foot ulcer can never be regarded as trivial. After initial diagnosis, early aggressive treatment should be instituted and the patient follows up until it is healed and has remained healed for at least a month. Foot ulcer is a sign of systemic disease, and successful management of DFU needs the expertise of a multidisciplinary team. All the components of multidisciplinary management of DFU are important.[15] Differentiation of neuropathic, neroischemic, and ischemic diabetic foot ulcer is very important for management and can be differentiated by the lab measures described above.

Table 3 | University of Texas Diabetic Wound Classification System Wound Depth Presence of infection or ischemia

	0	1	2	3
A	Pre- or postulcerative lesion with complete epithelialization	Superficial wound. No involvement of tendon, bone, or capsule.	Wound penetrates to tendon or capsule.	Wound penetrates to bone or joint.
B	Pre- or postulcerative lesion with complete epithelialization and infection.	Superficial wound. No involvement of tendon, bone, or capsule. Presence of infection.	Wound penetrates to tendon or capsule with infection.	Wound penetrates to bone or joint with infection.
C	Pre- or postulcerative lesion with complete epithelialization and ischemia.	Superficial wound. No involvement of tendon, bone, or capsule. Presence of ischemia.	Wound penetrates to tendon or capsule and ischemia.	Wound penetrates to bone or joint with ischemia.
D	Pre- or postulcerative lesion with complete epithelialization, infection, and ischemia.	Superficial wound. No involvement of tendon, bone, or capsule. Presence of infection and ischemia.	Wound penetrates to tendon or capsule with infection and ischemia.	Wound penetrates to bone or joint with infection and ischemia.

A full assessment of the patient is a prerequisite for managing DFU.

Treatment

The six principles of foot ulceration treatment are as follows:

1. Debridement
2. Pressure relief
3. Infection control
4. Revascularization (when appropriate)
5. Metabolic control
6. Educational control

Debridement

Debridement is an essential part of neuropathic ulcer treatment. Surgical debridement is required when there is extensive infection and tissue destruction.

Centers with high rate of debridement achieve better healing rates than centers that do not debride. However, neuroischemic ulcers should not be subjected to radical debridement.[16]

Hydroscalpel debridement

The VERSAJET II system enables a surgeon to precisely select, excise, and evacuate nonviable tissue, bacteria, and contaminants from wounds, burns, and soft tissue injuries.[17,18]

Ultrasonic-assisted wound treatment (UAW)

UAW is a noninvasive method using low-frequency ultrasound energy (25 kHZ) in combination with irrigation solution to clean/debride wounds and promote wound healing.

Maggot therapy

Biosurgical (larval) debridement is very effective in removing slough and necrotic tissue in neuroischemic ulcers (sterile maggots are not available in India).

Vacuum-assisted closure (VAC)

VAC consists of specialized dressing of adhesive, sterile open-cell foam. An evacuation tube is applied to the dressing and is attached to the VAC therapy device, which delivers regulated negative pressure to the wound site.[19]

Hyberbaric oxygen

It is the intermittent administration of 100% oxygen at higher-than-atmospheric pressure, that is, where oxygen dissolves in arterial blood plasma in increased amounts.

Topical wound oxygen

Oxygen has an integral role in wound healing. Physiologically, oxygen is involved with the enzymatic production of collagen and is therefore important for angiogenesis and granulation tissue. Adequate delivery of oxygen to the ulcer cells is therefore vital for healing.[20]

Platelet-rich plasma

Autologous platelet-rich plasma (PRP) may enhance wound healing through the formation of a platelet plug that provides both hemostasis and the secretion of biologically active proteins, including growth factors such as platelet-derived growth factor, transforming growth factor (TGF)-β, TGF-β2, and epidermal growth factor.[21]

Growth factors. They signal proteins that activate target cells to replicate or migrate. Action is complex and carefully controlled during the normal wound healing. Growth factors are mitogenic to target cells.

Dressings. Sterile nonadherent dressings should cover all open diabetic foot lesions to protect them from trauma, absorb exudates, reduce infection, and promote healing.[22]

Different types of dressings are available like foams, alginates, hydrogels, silver-impregnated dressings, and hydrocolloids. Irrigate with sterile saline. Immediate postoperative, use paraffin gauze. The frequency of dressing change depends upon amount of exudate. Use affordable and accessible materials to maintain moist wound environment.

DERMAGRAFT is approved as a class III medical device in the US and a class IV medical device in Canada for the treatment of DFUs. DERMAGRAFT is manufactured from human fibroblast cells derived from newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioresorbable scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors, and cytokines to create a three-dimensional human dermal substitute containing metabolically active, living cells.[23]

APLIGRAF is a living cell-based product from cells found in healthy human skins. It contains an outer layer of protective skin cells and an inner layer of collage-containing cells promotes healing of venous leg ulcers and DFUs.[24]

Medi Honey is made with active leptospermum honey. It comes in several forms: gel, paste, calcium alginate impregnated, and honey colloid with Tegaderm cover.

*Bone marrow-derived stem cell***.** Application of stem cells in the bone marrow aspirate (BMA) locally to the wound bed has shown promising results for treating lower extremity ulcer**s.**

Gene transfer therapy is promising as it may induce angiogenesis and inhibit restenosis, thereby restoring blood flow to ischemic tissue.

Pressure Relief

Relief of pressure is a basic principle of ulcer management. Bed rest with adequate heel protection is the most effective method of pressure relief but is impractical. So the ambulatory methods of off loading should be used.

In neuropathic foot ulcers the overall aim is to redistribute planter pressure, while in neuroischemic ulcers it is to protect the vulnerable margins of the foot.

Total contact cast (TCC) is the gold standard in offloading planter surface neuropathic DFU. Removable cast walker (Air Cast) is also used.

SK offloading is based on principles of Samdahan System; a square piece of foam is rolled and placed below the ulcer and secured with micropore tape. It is very easy and affordable and readily acceptable mode of offloading in treatment of planter surface DFUs in India.

Modified footwear. According to location of ulcer front, mid, and hindfoot offloading footwears with therapeutic insoles can be used. MCR, MCP, plastazote, poron, and silicone insoles can be used based on planter pressure measurements.

Infection Control

Debate continues on the use of systemic antibiotics. Antibiotic should be started at the slightest sign of infection in ulcer. Local antibiotics and antiseptics are having no role.

Antibiotic regime

Antibiotics for foot infections in patients with diabetes mellitus is began empirically (Table 4) and thereafter revised, based on results of cultures. Aminoglycosides should be avoided. Antibiotics are not recommended for clinically noninfected neuropathic foot ulcers.

Table 4 | Selected Antibiotics Regimens for Initial Empiric Therapy of Foot Infections in Patients with Diabetes Mellitus

Infection	Antimicrobial regimen
Non-limb-threatening	Cephalexin 500 mg po q6h Clindamycin 300 mg po q8h Amoxicillin-clavulanate (875/125 mg) one q12h Dicloxacillin 500 mg po q6h Levofloxacin 500–750 mg qd
Limb-threatening	Ceftriaxone 1 g IV daily plus clindamycin 450–600 mg IV q8h Ciprofloxacin 400 mg IV q12h plus clindamycin 450–600 mg IV q8h Ampicillin/sulbactam 3 g IV q4-6h Piperacillin/tazobactam 3.375 g IV q4h or 4.5 g IV q6h Fluoroquinolone IV plus metronidazole 500 mg IV q6h
Life-threatening	Impenem-cilastatin 500 mg IV q6h Piperacillin/tazobactam 4.5 g IV q6h plus gentamicin 1.5 mg/kg IV q8h Vancomycin 1 g IV q12h plus gentamicin plus metronidazole

Revascularization

Revascularization should be considered for all patients with peripheral vascular disease. All patients with vascular disease should be on anti-platelet therapy and smoking should be discouraged.

Metabolic Control

It is important to have good metabolic control in all diabetic foot ulcer patients and patients with Grade 2 and above ulcers should be preferably put on insulin.

Educational Control

Patient should be educated about the importance of footcare, like do not walk barefoot, inspect the feet daily, do not apply hot fomentation, use correct footwear, do not walk bearing weight on ulcerated/affected foot or after surgery.

Recent Advances

Recent advances in both diagnosis and management of diabetic foot include foot scan (inshoe technique), use of growth factors (platelet derived growth factor [PDGF]),vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), keratinocyte growth factor (KGF), epidermal growth factor (EGF), hyperbaric oxygen therapy (HBOT), vacuum-assisted closure of wound, ultrasound-assisted wound debridement, foot surgeries for unstable CF, skin equivalents, and stem cell therapy.

Conclusion

Numerous studies have shown that healing foot ulcers in the diabetic population costs the healthcare system of any country much less overall, in the long term, than amputating the affected foot.[25] Amputation rates will be significantly reduced if the following protocol is implemented, that is, inspection of feet and footwear during patient's regular visits, use of preventive foot and shoe care in high-risk feet, implementation of a multifactorial and multidisciplinary approach to care for established foot ulcers, early diagnosis of peripheral vascular disease and vascular intervention if required, continuous follow-up of patients with previous foot ulcers, and registration of amputations and foot ulcers.

The absolute goal of treatment of the diabetic foot is the prevention of ulceration, the prevention of the recurrence of ulceration and, ultimately, the reduction of amputation. Every 20 seconds a limb is lost somewhere in the world because of diabetes. There has to be a radical change in the way we assess and treat these patients, and knowledge of current guidelines and protocols is essential if we are to achieve this.

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"Strong minds discuss ideas, average minds discuss events, weak minds discuss people."

— Socrates