REVIEW ARTICLE

Diabetic Foot

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INTRODUCTION:

Diabetes has exhibited a fast growth as a public health challenge and a budding epidemic across low-and-middle-income countries like India.[1] It was projected that the overall prevalence of diabetes will increase from 9.3% (463 million) in 2019 to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[2] According to an estimate, India will hold 69.9 million diabetics by 2025 with still huge numbers yet to be diagnosed.[1,3] The long duration of diabetes carries the risk of developing multiple complications, among which foot ulceration (DFU) or the 'diabetic foot' is a major complication.[4] Diabetes for a decade is considered a significant duration to develop a DFU.[5] However, the course of disease- as poor/well-controlled- will change the outcome.[6] DFU is an aftereffect of combined neuro-vascular compromise in the wake of some trivial trauma and poor glycaemic control.[4] It can impair the quality of life, affect social participation, and interferes with livelihood.[7] Also economic burdens of diabetic extremity care are as high as cancer.[8]

Studies have indicated that diabetic patients have a 25% lifetime risk of developing a foot ulcer.[9] About 6% of people with diabetes suffer from DFU, ranging from infection, ulceration, destruction of tissues, or gangrene.[10] The global incidence of diabetic foot ulcers is nearly 3%, with the reported incidence in developed nations like the U.S. and the U.K. as high as 10%.[11] Major issue in DFU is that an ulcer has an increased risk of progression that may ultimately result in amputation; an ulcer is seen as a predecessor in up to 85% of amputations.[11] It is estimated that 0.03% to 1.5% of DFUs eventually require amputation, resulting in significant disability and an increased mortality rate.[12,13] Perhaps, most ulcers can be prevented with good foot care and screening for risk factors.[9] At least 40% of amputations in diabetic patients can be avoided with a team approach to wound care.[14] In low- and middle-income countries like ours, barefoot walking, lack of awareness, delay in seeking medical care, and shortage of trained healthcare providers and foot care services are common factors that add to the burden of foot disease.[15]

PATHOGENESIS

DFUs result from the synchronous action of multiple factors and causes.[16,17] The patient would have other diabetic complications in tandem with the ulcer.[18] Peripheral neuropathy and peripheral vascular disease are the prime underlying causes of DFU.[19] Poorly controlled diabetes is pivotal in developing neuropathy and peripheral vascular disease through complex metabolic pathways.[20] A study has indicated that diabetes-related peripheral neuropathy and peripheral vascular disease have a prevalence of 0.003-2.8% and 0.01-0.4%, respectively.[12] Diabetes is also implicated in Charcot arthropathy (0.08% and 13%), which involves progressive destruction of the bones, joints, and

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soft tissues.[21,22] It results from a combination of motor, autonomic, and sensory neuropathies in which muscle and joint laxity lead to changes in the arches of the foot. Further, the autonomic denervation leads to bone demineralization via the impairment of vascular smooth muscle, which leads to an increase in blood flow to the bone with significant osteolysis.[23] A combination of neuropathy, abnormal loading of foot, repeated micro trauma, and metabolic abnormalities of bone lead to inflammation, osteolysis, fractures, dislocations, and deformities. [24]

Neuropathy

Neuropathy in diabetes develops because of hyperglycemia-induced metabolic abnormalities.[25,26,27] Polyol pathway is one of the commonly attributed mechanisms of action.[26] Hyperglycemia increases the activity of the enzymes aldose reductase and sorbitol dehydrogenase, causing the conversion of intracellular glucose to sorbitol and fructose. These sugar products reduce the synthesis of nerve cell myoinositol required for normal neuron conduction.

Furthermore, glucose conversion depletes cellular stores of nicotinamide adenine dinucleotide phosphate (NADP), required for synthesizing the vasodilator nitric oxide (NO) and the detoxification of reactive oxygen species. So, the net result is enhanced oxidative stress on the nerve cell and increased vasoconstriction-induced ischemia, both supporting neuronal injury and death. These metabolic abnormalities and oxidative stress also stimulate the abnormal glycation of nerve cell proteins and the inappropriate activation of protein kinase C, ensuing additional nerve dysfunction and ischemia.[23]

Neuropathy in diabetic patients presents as motor, autonomic, and sensory.[19] Denervation of the foot's intrinsic muscles results in the abnormal kinematics (flexion/extension) of the involved foot. It gradually leads to anatomic deformities with abnormal bony prominences and pressure points, causing skin breakdown, cracks, and ulcers.[23] Autonomic neuropathy results in decreased sweat/sebaceous gland activity. Consequently, the foot loses its natural moisturizing capability, and the skin becomes dry and susceptible to cracks with subsequent infection and ulceration.[23] The loss of sensation as a part of peripheral neuropathy exacerbates the development of ulcerations. More than 60% of DFUs have an underlying neuropathy.[19,28] When trauma, which may be trivial, occurs to the foot, patients are unaware of the insult. Consequently, wounds go unnoticed and gradually worsen as the exact part is continually subjected to repetitive injury due to pressure and shear from ambulation and weight bearing. So, it would not be discovered until late. [4,23]

Vascular Disease

In about half of the DFUs, Peripheral vascular disease is a contributing factor.[29,30] commonly affected are the tibial and peroneal arteries. Hyperglycemia leads to endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries, with the resultant fall in endothelium-derived vasodilators causing vasoconstriction.[25] Additionally, hyperglycemia is associated with a rise in thromboxane A^2, a vasoconstrictor and platelet aggregation agonist, resulting in an enhanced risk for plasma hypercoagulability. There are also potential changes in the vascular extracellular matrix causing stenosis of the arterial lumen.[31] Furthermore, other triggering factors like smoking, hypertension, and hyperlipidemia are common in people with diabetes and contribute to PVD.[16] Acting in unison, all this leads to occlusive arterial disease causing lower limb ischemia with an increased risk of ulceration.[23]

ASSESSMENT OF DIABETIC FOOT ULCERS

A complete history will aid in assessing the risk for foot ulceration. In addition, history should take glycaemic control and previous ulceration or amputation.[15] The history should inquire about any neuropathic symptoms and other complications of diabetes like retinopathy and nephropathy. Finally, history regarding smoking is essential because smoking is linked to developing neuropathic and vascular diseases.

The American Diabetes Association (ADA) has specified the recommended components of foot examinations for diabetic patients.[32] A thorough foot examination is indispensable for early disease detection.[15] The barefoot should be inspected well in a well-lit room. The footwear should be properly assessed as inappropriate shoes pose a risk for ulceration.[23] Examination is performed for lesions such as fungal infection, cracks and skin fissures, deformed nails, macerated web spaces, calluses, and deformities such as hammer toes, claw toes, and pes cavus, which increase the risk of ulceration. The temperature of the feet should be felt with the dorsum of the examiner's hand. A cold foot or

difference in temperature between the two feet would suggest ischemia, and increased warmth with redness and swelling might suggest inflammation such as acute Charcot foot or cellulitis.[15] The likelihood of osteomyelitis is considered in the presence of exposed underlying bone or bone that can be palpated with a blunt probe. Based on this initial assessment, patients can be categorized as having a low, moderate, or high risk of diabetic foot (Table 1).[24]

Table1: Risk Assessment[24]

Low risk	Moderate risk	High risk	Active diabetic foot problem
No risk factors present except callus alone	Deformity or Neuropathy or Non-critical limb ischaemia	Previous ulceration or Previous amputation or On renal replacement therapy or Neuropathy and non-critical limb ischaemia together or Neuropathy in combination with callus and/or deformity or Non-critical limb ischaemia in combination with callus and/or deformity	Ulceration or Spreading infection or Critical limb ischaemia or Gangrene or Suspicion of an acute Charcot arthropathy, or Unexplained hot, red, swollen foot with or without pain

SCREENING

Screening for peripheral neuropathy and peripheral arterial disease can help identify patients at risk of foot ulcers.[15]

Peripheral Neuropathy, The loss of protective sensation in the foot, has been identified as a significant risk factor for developing ulceration. Screening aims to identify patients with loss of protective sensation. Most guidelines recommend the 10 g monofilament for neuropathy assessment in diabetic patients.[24,33] This test is portable, easy to perform, and cheap.[34,35] This monofilament exerts a 10 g buckling force when it bends. The monofilament is tested on various sites along the plantar aspect of the toes, the ball of the foot, and between the great and second toe. However, the areas of the callus should not be tested.[30] An inability to sense a 10 g pressure is the consensus definition of loss of protective sensation and is considered reflective of an ulcer risk.[36] Despite its widespread use, the accuracy of the test in diagnosing neuropathy is variable.[37] This test might be combined with another test like a biothesiometer or a graduated tuning fork (Rydel Seiffer) to assess vibration perception threshold to screen for neuropathy.[38,39]

Peripheral Arterial Disease History of intermittent claudication and rest pain, which suggest peripheral arterial disease, should be inquired about.[40] Claudication, loss of hair, and the presence of pale, thin, shiny, or cool skin are physical findings suggestive of potential ischemia. In examining for vascular abnormalities of the foot, the presence/ absence of the dorsalis pedis and posterior tibial pulses should be ensured by palpation.[41,42] The ankle-brachial index is an adjunct measure to diagnose peripheral arterial disease in the outpatient setting.[40,43] It is the ratio of the highest systolic blood pressure at the ankle to the systolic blood pressure at the arm and is measured using a handheld Doppler device.[33] Ratios below 0.91 are suggestive of obstruction (Table 2).[44] It elucidates on grading the severity of obstruction. People with diabetes often have falsely raised ankle-brachial index levels due to poor compressibility from calcified arteries or aortoiliac stenosis.[43,44] Measurement of the ankle-brachial index is user dependent. Furthermore, availability of equipment, time constraints, and lack of training are reported as significant barriers to ankle-brachial index testing in primary care.[45,46,47] If there is a strong suspicion of vascular disease, the patient should undergo vascular imaging as an alternate testing method to determine the extent of the disease and possible ischemia.[16]

Table 2: Ankle Brachial Index

Interpretation of the Severity of Peripheral Arterial Disease [44]	
0.91-1.3	Normal
0.70-0.90	Mild Obstruction
0.40-0.69	Moderate Obstruction
<0.40	Severe Obstruction
>1.3	Poorly Compressible Vessel

CLASSIFICATION OF DIABETIC FOOT ULCERS

If an ulcer is discovered, the description should include characteristics of the ulcer, including size, depth, appearance, and location.[48] There are many classification systems used to depict ulcers that can aid in developing a standardized management method. These classification systems are based on a variety of physical findings.[23]

One of the most popular classification systems is the Wagner Ulcer Classification System, based on wound depth and the extent of tissue necrosis (Table 3).[49] Several authors have noted a disadvantage of this system in that it only accounts for wound depth and appearance and does not

consider the presence of ischemia or infection.[30,50] To circumvent this deficiency, the University of Texas system is another classification system that addresses ulcer depth as well as the presence of infection and ischemia (Table 4).[51] Wounds of increasing grade and stage are less likely to heal without vascular repair or amputation.[50]

Table 3: Wagner's Classification for Diabetic Foot [49]

Grade	Description of Lesion
Grade 0	High risk foot and no ulceration
Grade 1	Superficial ulcer
Grade 2	Deep ulcer; Ulcer extension involving ligament, tendon, joint capsule, or fascia, no bony involvement with no abscess or osteomyelitis
Grade 3	Deep ulcer with bony involvement; abscess or osteomyelitis
Grade 4	Gangrene to portion of forefoot
Grade 5	Extensive gangrene involving whole of foot

Table 4: The University of Texas Staging System for Diabetic Foot Ulcers[51]

Stage	Grade 0	Grade I	Grade II	Grade III
A	Pre- or post - ulcerative lesion completely epithelialized	Superficial ulcer, not involving tendon capsule or bone	Ulcer penetrating to tendon or capsule	Ulcer penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia
Score: Grade_____Stage_____				

MANAGEMENT MODALITIES

The results of the foot evaluation aid in developing an appropriate management plan with several facets of care.[52] Management is largely evidence-based, encompassing optimization of blood sugars, maintenance of co-morbid conditions, debridement of dead/necrotic tissue, enhancement of blood flow, and proper foot care.

Therapeutic footwear is a promising technique- it diminishes the risk of recurrence of ulcers, especially in those with foot deformities.[53] Occlusive footwear leads to sweating and can predispose to fungal infection, particularly in tropical countries.[54,55] Ideal footwear should have a wide toe box, soft cushioned soles, extra depth to accommodate orthoses if required, and laces or Velcro for fitting and adjustments. Patients with ulcers on the sole at the forefoot or heel may be offered offloading footwear to allow ulcer healing and prevent a recurrence. It is recognized that there is poor patient compliance to prescribed footwear, notably at home, where they are more active.[56]

Offloading and debridement are regarded as fundamental tools in the healing of DFUs.[57] The aim of offloading is to redistribute the pressure (ulcers sites and pressure points at risk) to a broader area of contact.[58] There are several methods/techniques of pressure alleviation, comprising surgical shoes, immovable glass splints, total contact splints, total contact casting, half shoes, removable cast walkers, wheelchairs, and crutches.[59,60,61] Each of these modalities has its pros and cons, and factors such as the general condition of the wound, requisite frequency of wound examination, presence/absence of infection, and the prospect for patient compliance might determine which modality suits the patient best.[62]

A more invasive treatment option is the debridement of necrotic or unhealthy tissue. Ulcers can be superficial or deep. Superficial ulcers are debrided till bleeding starts- a sign of healthy tissue. Deep ulceration can be the aftermath of improper treatment of an ulcer or an infected gangrenous condition per se.[13] The debridement should incorporate the adjoining excision callus, which would offload the pressure points on the callus. Also, the necrotic burden and bacterial load are brought down with a clear assessment of the deeper tissue involvement.[63] In addition, it furnishes relevant tissue for culture/sensitivity. Vital to note here is that the tissue from the base of the ulcer, following the debridement, provides more valid and specific results than a superficial wound swab.[64]

The wound dressings continue to retain their significance in diabetic wound care management. Dressings should be changed daily with proper wound assessment.[65] An ideal dressing should dispense a moist wound environment, absorb excessive exudates, and reduce the infection risk.[66] A wide array of dressing types is available. The characteristics of a specific type can be optimal based on the condition of the individual wound. There are not many studies in the literature to support or undermine the use of a dressing over another, and none of them has demonstrated any significant outcome differences.[53,65,67] saline-soaked gauze dressings are cheap, well tolerated, and provide a moist wound environment. Foam and alginate dressings, being highly absorbent, are helpful in heavily exudative wounds.

Hydrogel has been shown to have higher cure rates of DFU compared to gauze dressings.[61] Topical chemical debriding agents (enzymes) are also available for use. In indolent cases, maggot therapy is used to debride dead tissue, leaving behind only the healing tissue.[68,69] In chronic wounds, maggot therapy stimulates rapid healing by shortening healing time.[70] Other significant concerns in DFU management are infection control and neuropathic pain. Early optimization of blood sugars effectively prevents neuropathy, but the reversal of neuropathy by reasonable glycaemic control is not evidenced in the literature.[71] Optimal blood sugar and glycated haemoglobin (HbA1c) can prevent or impede the progression of peripheral neuropathy.[72,73] For neuropathic pain, multiple drugs and drug combinations have been tried, including antidepressants, anticonvulsants, or opioids combined with gabapentin. Among these, only duloxetine and gabapentin are approved by the Food and Drug Administration (FDA).[53] The surgeon needs to be sceptical of the potential development of infections. The selection of appropriate drugs should rely on the culture/sensitivity results of the wound.[53] Neuropathy and foot deformities are considered potential risks for superimposed infection in otherwise noninfected ulcers.[74] Though Gram-positive cocci are most frequently isolated, the chronic ones or those treated earlier demonstrate polymicrobial growth, together with gram-negative rods and anaerobes.

Pseudomonas, for instance, is often cultured from wounds that have been treated with wet dressings. Anaerobic bacteria are often cultured from ulcers with ischemic necrosis or deep tissue involvement. Antibiotic-resistant organisms such as methicillin-resistant Staphylococcus aureus (MRSA) are frequently found in patients previously treated with antibiotic therapy or with a recent history of hospitalization. The selection of appropriate antimicrobial treatment, including the drug, route of administration, and need for inpatient or outpatient treatment, will be determined in part by the severity of the infection. Admission is required in case of systemic signs of severe infection and/or to rule out any deep occult septic focus, inability to provide proper self-care, poor compliance with antimicrobial therapy, or those who require close monitoring for treatment response.[64,75] Other patients can be managed at home with regular follow-up visits.[76] Common antimicrobial agents include cephalosporins, fluoroquinolones, and penicillin/beta-lactamase inhibitors. Information about various drugs in use with their dosage, duration of therapy, and clinical effectiveness based on severity are well published.[63,64] In the case of osteomyelitis of the underlying bone, surgical debridement of the affected bone, along with an extensive course of antibiotic therapy, is instituted.[16] Patients with evidence of decreased distal blood flow or ulcer that does not progress toward healing with appropriate treatment may need revascularization.[4,23] Favourable long-term results with about 90% 10-year limb-salvage rate have been demonstrated with surgical bypass.[59,60] Transluminal angioplasty of the iliac arteries together with surgical bypass has shown promising efficacy in diabetic patients.[77] Endovascular revascularisation performed by a radiologist can also be undertaken to reduce the need for amputation.[78]

Several other adjunctive wound care therapies are investigated or practised for managing diabetic foot ulcers. Skin substitutes promote wound healing by activating cytokines and dermal matrix components that stimulate tissue growth.[79,80] Recombinant platelet-derived growth factor has been shown to promote the recovery of the ulcer.[81] G-CSF has been found to enhance the activity of neutrophils in diabetic patients.[53,82] A meta-analysis on the use of G-CSF revealed that, although it did not significantly settle infection, the risk of amputation and the need for other surgical procedures get reduced.[23,83] However, a word of caution here is that most of these modalities are not recommended for their routine use in treating diabetic wounds.[63]

Negative Pressure Wound Therapy (NPWT) is another effective treatment modality, mostly reserved for when other treatments fail to show optimal results.[53,84] Studies have demonstrated improved wound healing with reduced amputation rates.[85,86] Another adjunctive treatment modality is hyperbaric oxygen therapy (HBOT). Wagner Grade 3 wounds that have failed to resolve after a 4-week course of standard treatment are considered appropriate.[4]

RECURRENCE AND PREVENTION

The current approach to treatment has shifted to the multidisciplinary model. An interdisciplinary approach has demonstrated reduced rates of significant amputations.[87]

Delayed or no referrals, poor patient compliance, and poor communication between physicians contribute to the prolonged healing process.[88] Here, it is essential to underline that the 5-year survival rate is estimated to be 24.6% in those with a history of DFU.[89] Overall, optimization of blood sugars is known to favour the prognosis of complications in diabetes.[90]

Poor glycaemic control inevitably increases the wound healing period per se.[91] Patient education regarding the importance of maintaining reasonable glycemic control, wearing appropriate footwear, avoiding trauma, and performing frequent self-examinations is of utmost importance.[63] Studies show that structured, well-organized (repetitive) patient education schemes with preventive strategies help prevent foot complications.[56] Thus, the International Working Group on the Diabetic Foot recommends patient education to revamp foot care knowledge and behaviour.[33]

For healed DFU, the 5-year cumulative rate of ulcer recurrence has been stated to be 66%, and the amputation rate 12%.[92] This recurrence is common within three years from the previous ulcer.[91,93] This highlights the importance of identifying potential risk factors. Therefore, at least an annual foot examination to detect the predisposing conditions is recommended.[30] This will help limit the occurrence rate, delay the occurrence, and reduce the recurrence rate. Limiting the risk factors by timely referral to foot care services serve to avoid gangrene, amputation, and/or death, along with decreased inpatient hospital admissions and expenditures.[24]

According to a study focused on the prognosis of diabetic foot ulcers, ulcer outcome is influenced by the features of the ulcer, epidemiological factors, and other comorbidities.[94] These elements comprise perfusion status, wound dimensions (especially depth), infections, and sensibility.[51,95] Another study recognized underlying osteomyelitis, poor glycaemic control, and plantar location of the ulcer as independent risk factors for recurrence.[93] Other factors incriminated for delayed healing are hypertension, size of ulcer $\geq 2cm^2$, previous amputation, and ulceration on the sole.[96]

A risk classification system developed by the Foot Care Interest Group of the ADA has outlined the recommendations regarding the need for specialist referral and/or suggested follow-up protocol (Table 5).[30] Lowest risk category patients need education on general foot care with yearly follow-up. Higher risk categories are more reasonable to do well with specialist care and more frequent follow-up visits.[23]

Table 5:Risk Classification System of the Task Force of the Foot Care Interest Group of the ADA[30]

Risk Category	Definition	Treatment Recommendations	Suggested Follow-up
0	No LOPS, no PAD, no deformity	Consider patient education on foot care, including information on appropriate footwear.	Annually (by generalist and/or specialist
1	LOPS ± deformity	Consider prescriptive or accommodative footwear. Consider prophylactic surgery if deformity is not able to be safely accommodated in shoes. Continue patient education.	Every 3 –6 months (by generalist or specialist)
2	PAD ± LOPS	Consider the use of accommodativefootwear. Consider a vascular consultation for combined follow-up.	Every 2 –3 months (by specialist)
3	History of ulcer or amputation	Consider patient education onfoot care. Consider vascular consultation for combined follow-up if PAD present.	Every 1 –2 months (by specialist)

LOPS = loss of protective sensation; PAD = peripheral arterial disease.

Evidence for the effectiveness of patient education on foot care is lacking. A Cochrane review of randomized controlled trials concluded that brief foot care education alone positively influences patient knowledge and behaviour in the short term. Still, it is ineffective in preventing diabetic foot ulcers. Teaching in a structured, organized, and repetitive manner, combined with preventive interventions, may avoid foot problems.[56] although the International Working Group on the Diabetic Foot acknowledges the limited evidence on the long-term efficacy of patient education, it recommends some form of patient education to improve their foot care knowledge and behaviour.[33]

CONCLUSION

Patients with diabetes are at an increased risk of developing foot ulcers. The treatment strategy comprises offloading, debridement, appropriate dressings, and antibiotics, if needed, based on the culture results. If there is evidence of ischemia, revascularization may be indicated to restore arterial blood flow for limb salvage. The periodic foot appraisals in diabetic patients with the inclusion of appropriate basis and specialized care scale down the risk of ulceration with its attendant morbidities.

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