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DIABETIC FOOT ULCER: AN UPDATED REVIEW 2020

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ABSTRACT

Diabetic foot ulcers (DFU) are lesions of all skin, necrosis or gangrene layers that happen in the sole of the feet in patients with diabetes mellitus (DM). It caused mainly by: (a) causative factor (peripheral neuropathy, high plantar foot pressure and trauma); (b) contributing factors (atherosclerosis and diabetes) and can be determined by deep anamnesis and physical examination. It affects nearly about 6% of people with diabetes and includes infection, ulceration or destruction of tissues of the foot and between 0.03% and 1.5% of patients with diabetic foot require an amputation. It can impair patients health related quality of life and affect social interaction. Most ulcers can be prevented with good foot care and repairing the cause of ulcer, good wound care and prevention of recurrence. Basic therapy includes necrotomy/debridement, decreasing the load/pressure on the offensive area, manage the infection by diagnosing the type of bacteria, providing adequate antibiotics and ulcer treatment using wound dressing clean and moist. The main contributing factor that leads to DFU includes peripheral arterial disease, neuropathy, previous amputation and infection. Mortality and morbidity can be decreased by early recognition. We provide an update on the therapeutic management including advanced therapies of diabetic foot.

KEYWORDS: Diabetic foot ulcer, diabetes, amputation, debridement.

INTRODUCTION

Diabetes mellitus (DM) is one of the majaor health services issues and it's a worldwide menace to public health that has grown dramatically over the previous two centuries.[1,2]

According to epidemiological studies, the number of DM patients increased from approximately 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and more than 360 million people will have DM by 2030 if the situation continues.[3,4] DM patients are susceptible to various complications such as diabetic foot ulcer(DFU). DFU is a prevalent complication of DM, which in past decades has shown a growing trend.[5-7] DFU is currently regarded as a significant source of morbidity and a leading cause of hospitalization in diabetic patients.[1,5,8,9] It is estimated that DFU accounts for approximately 20% of hospital admissions among DM patients.[10] On the other side, once the DFU has evolved, there is an enhanced risk of ulcer development which can eventually leads to amputation.[11] Moreover, every 30s of one leg is revealed to be amputated globally owing to DFU.[12] In addition, DFU is liable for significant emotional and physical distress, productivity and financial losses that reduce quality of life.[13]

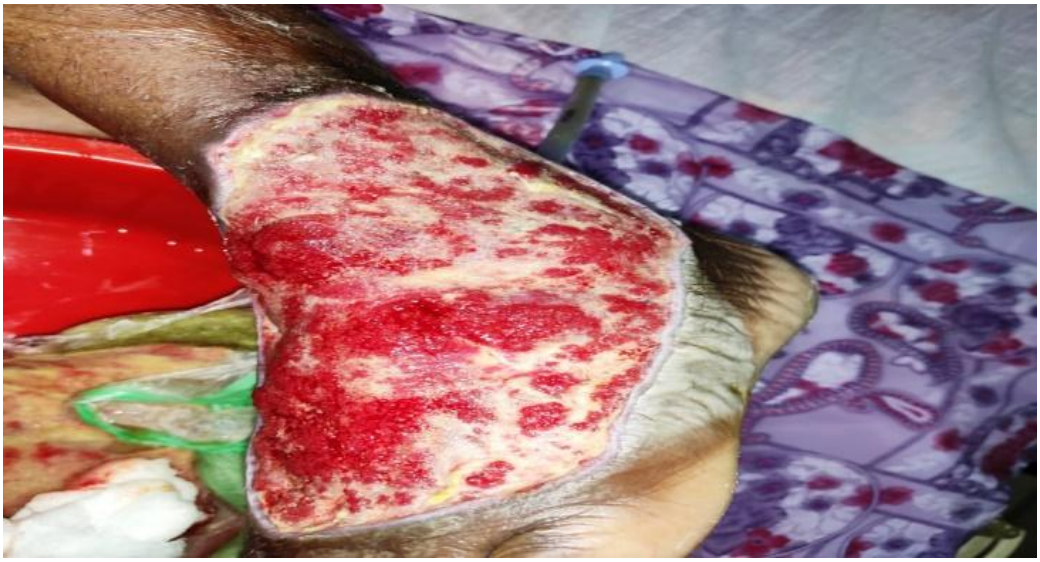

Figure no. 1: Diabetic Foot Ulcer on left leg.

Etiology

There are several factors that can cause diabetic foot ulcers to develop in patients with diabetes, can be divided into two major factors namely.[11,12,14-25]

1. Causative factor

Peripheral neuropathy (sensory, motor and autonomic)

Sensory neuropathy is generally relatively deep (> 50%) before a loss of protective sensation leading to susceptibility to physical and thermal trauma, thus increasing the danger of foot ulcers. Not only the sensation of pain and pressure are lost, but also the proprioception of the sensation of foot position also vanished. Motor neuropathy influences all the muscles in the

legs, leading in the protrusion of abnormal bones, changing ordinary foot structure, unique deformation such as hammer toe and hallux rigidus. With regard to autonomic neuropathy or autosimpatectomy, characterized by dry skin, no sweating and increased secondary capillary refill due to skin arteriovenous shorts, fissures, skin crust, all render the foot susceptible to minimal trauma.

Elevated foot plantar pressure

This scenario relates to two things: joint mobility constraints (ankle, subtalar and first metatarsophalangeal joints) and foot deformities. In patients with peripheral neuropathy, 28% with elevated plantar pressure, a foot ulcer compared to patients without elevated plantar pressure will occur within 2.5 years.

Trauma

In particular recurrent trauma; 21% foot friction trauma, 11% foot injury (mostly due to fall), 4% cellulitis owing to complications of tineapedis and 4% owing to fingernail cutting errors.

2. Contributive factor

Atherosclerosis

The most significant contributing factor is atherosclerosis owing to peripheral vascular disease, particularly in the blood vessels below the knee. The risk of ulcers twice as elevated in patients with diabetes as in patients without diabetes.

Diabetes

Diabetes contributes to intrinsic wound recovery, including cross linking disorders of collagen, functional disorders of the metricoproteniase matrix and immunological disorders, particularly impaired PMN function. Furthermore, diabetes have greater rates of onychomycosis and tinea infections, making skin and infections easy to peel. In DM, characterized by sustained hyperglycemia and increased inflammatory mediators, causing an inflammatory response that leads to chronic inflammation, but this is considered to be low grade inflammation because hyperglycemia leads to impaired cellular defence mechanisms. Inflammation and neovascularisation are essential for wound healing, but the interaction of molecular cells be sequential, self-limited and tightly regulated. Acute inflammatory reactions in DM are regarded weak and angiogenesis interrupted leading to wound healing disorders.

Pathogenesis

Diabetic foot ulcer is the result of a complicated combination of different risk factors such as peripheral neuropathy, peripheral vascular disease, foot deformities, arterial insufficiency, trauma and impaired infection resistance.[26, 27]

Neuropathy

Neuropathy is a disease that affects the nerves, causing sensation impairment, movement and other health aspects depending on the affected nerve. One of the main causes is peripheral neuropathy in diabetes.[28] Up to 66% of patients with diabetes in the reduced extremity face peripheral neuropathy.[29] Studies have shown that metabolic anomalies caused by hyperglycemia cause neuropathy.[30] There are several other factors that account for the origin of neuropathy.[31, 32] defects in the metabolism of fatty acid,[33] activation of protein kinase-C pathway,[34] formation of sophisticated glycated end products,[35] Myoinisitol,[36] polyol pathway,[37] development of nerve growth factor,[38] and development of neural tissue antibodies.[39]

The four primary mechanisms that cause hyperglycemic nerve damage are high levels of sophisticated glycated intracellular end products, activation of protein kinase C, increased flux of hexosamine and the polyol pathway.[40] Neuropathy in patients with diabetes is manifested in motor, autonomic and sensory divisions of the nervous system. In motor neuropathy, damage to motor nerves changes the body's capacity to coordinate movements and the formation of foot deformity, Charcot's foot and hammerhead toes. Motor neuropathy causes atrophy in the foot muscles, resulting in changes in the foot anatomy that cause osteomyelitis.[41] Sensory neuropathy leads to wreckage of sensory nerves present in extremities. Recurrent foot injuries are the result of sensory neuropathy that interferes with the integrity of the skin and provides a feasible path for microbial invasion that leads to unhealed wounds that form chronic ulcer at serious phases. Loss of protective sensation leads to ulcers triggered by improper shoes, heat exposure and damage caused by foreign agents.[42] Autonomic neuropathy leads to deportation in functions of sweat and sebaceous glands in foot which in turn leads to skin drying and fissure predisposition. As a consequence, the natural moisturising skin of the foot is lost, the surrounding skin become more susceptible to breaks and infection development.[43] Motor, sensory and autonomic disturbances owing to neuropathy lead to skin lose.[44] Neuropathy predisposes the foot to infection and angiopathy impacts the result.[45]

Peripheral vascular disease

Peripheral vascular disease (PVD) is a lower extremity occlusive atherosclerotic disease. Diabetes is a significant risk factor for PVD.[46] PVD is a significant cause of prejudiced to foot ulcer development in about 50% of cases. In type 2 diabetes, it accounts for 70% of death.[47] Diabetes patients have a higher incidence of atherosclerosis, thickening of capillary basement membranes, hardening of arteriolar walls and proliferation of endothelia. Acute or chronic ischemia results in atherosclerotic blockages of large and medium sized arteries, such are femoropliteal and aortoiliac vessels. Ulcers can grow and immediately advance to gangrene owing to insufficient blood flow in combination with artery disease.[48] Diabetics have low blood supply, so peripheral ischemia branches out ulceration. Improper blood supply to the periphery contributes to bad wound healing that aggravates the situation.[49]

Reduced arterial perfusion leads peripheral pulses to decrease and patients are at danger of ulceration, infection with impaired healing rates and ultimately chronic gangrene and amputation.[50] Epidemiological studies indicate that lipids, lipoproteins specifically may contribute to PVD as well as hypertension, smoking and hyperglycemia are also important predictive risk factors.[51]

Other risk factors

Diabetic foot ulcers (DFUs) are correlated with several contributing factors. Studies testified history of ulceration or amputation, foot pressure, peripheral edema, patients with weak socio-economic background,[52] plantar callus formation,[53] ischemia,[54] nephropathy, retinopathy, weak glucose control, old age and prolonged diabetes[55] as important predisposing factors causing DFUs. It is also noted that health care and education are a significant risk factor for foot ulcer,[56]

Pathophysiology

In DM patients, the primary risk of diabetic foot ulcers occurring and developing, namely peripheral neuropathy, peripheral vascular disease, and disturbance of reaction to infection. In addition, there is a wound healing disorder in DM that increases the risk of infection.[43, 57]

DM manifestations of neuropathy against motor, sensory and autonomic. Damage to the leg muscles innervation creates an imbalance between bending and leg extension, resulting in deformity and change in pressure point. It will gradually cause damage to the skin that change into ulcers. Autonomic neuropathy reduces the activity of oil glands and sweat,

thereby reducing foot moisture and causing injury. Sensory neuropathy lowers the threshold for pain so that it is sometimes unaware of the wound's existence until the wound worsens.[43]

Hyperglycemia causes endothelial dysfunction as well as reduced endothelial vasodilator production resulting in constriction. Hyperglycemia in DM improves thromboxane A2, namely vasokontrikotor and platelet aggregates, leading in an enhanced risk of hypercoagulability of the plasma. Hypertension and dyslipidaemia also lead to the development of arterial peripheral disease. The above explanation will lead to occlusive arterial disease that causes reduced extremity ischemia and increases ulcer risk. The formed ulcers will readily become infected, develop into gangrene and end up with a lower amputation of the leg (below amputation of the knee).[43,57]

In DM, the peripheral healing capacity of soft tissue is reducing, owing to ulcers. In diabetes, particularly in the advanced stage where skin tissue structure, nerves, blood vessels and other supporting tissues have been damaged, so blood glucose control is no longer sufficient to fix them. Slow wound healing in DM will improve the risk of complications of wound that will slow wound healing further. These are the complications (including cellulitis, abscesses, and osteomyelitis), gangrene, and septicaemia.[57,58]

Classification

A comprehensive elucidation of features of ulcer, such as depth, size, appearance and location, provides mapping of progress during therapy. The assessment should determine the ulcers's etiology and verify if the lesion is neuropathic, ischemic or neuro-ischemic.[59]

Different classification systems have been suggested to evaluate the seriousness of diabetic foot lesion attempting to include various ulcer characteristics including ulcer size, depth, ischemia, infection and neuropathy.[60] In general, poor clinical outcomes are correlated with peripheral vascular disease, increasing the depth of the wound and infection. It also appears that these comorbidities progressive cumulative impact contributes to a higher probability of diabetic foot ulcer leading to lower limb amputation.[61] Therefore, it is very essential to have a correct classification scheme that can describe ulcer features that will assist to plan strategies for treating diabetic foot lesions. Many wound classification systems that were developed are based on parameters such as extent of infection, neuropathy, ischemia, depth of tissue loss and location.[62] are addressed below:-

a. Wagner-Meggit Classification system
b. Brodsky Depth- ischemic Classification
c. University of Texas Classification
d. International Working Group Classification

Wagner- meggit classification

Wagner-Meggit scheme is one of the most frequently used classification scheme. Although it has been designed for dysvascular foot, it has been in use for 25 years.[63] It is a six degree classification system that takes into account ulcer depth, gangrene presence,[62, 63] and tissue necrosis level.[64] Although Wagner's classification is one of the most commonly used classification systems, it does not take significant clinical parameters such as ischemia, infection and other comorbid factors into consideration.[65] (Table 1).

Table 1: Wagner-Meggit classification system.

Grade	Foot lesion
0	No open lesions or cellulitis
1	Superficial ulcers
2	Deep ulcer with up to tendons and joint tissues
3	Deep ulcers with abscess, osteomyelitis and joint sepsis
4	Local gangrene forefoot or heal
5	Gangrene of entire foot

Depth ischemic classification

This classification is a Wagner- Meggit system modification. The aim of this classification scheme is to make the classification more precise, balanced and easier to differentiated between wound and foot vascularity, to clarify the difference between grade 2 and 3 and to improve the therapy correlation to grade.[66] (Table 2)

Table 2: Depth ischemic classification system.

Depth grade	Definition	Ischemia grade	Definition
0	At risk, foot with previous ulcer that may cause new ulcer	A	No ischemia
1	Superficial non-infected ulcer	B	Ischemia no gangrene
2	Deep ulcer with tendon or joint exposed (+/-)infection	C	Partial forefoot gangrene
3	Extensive ulcer with bone exposed or deep abscess	D	Total foot gangrene

University of texas classification

By taking into account the parameters not included in the Wagner classification system, the Wagner grading system is effectively modified. The classification scheme of the University of Texas Antanio (UTSA) evaluates diabetic foot lesion by depth, wound infection, and lower limb ischemia. In this ischemia, the grading is based on the depth of the lesion and the stages are categorized according to the presence of ischemia, wound bio burden or combination of the two excluding neuropathy.[67] Grade (0-3) and stages (A-D) are available. Higher grade wounds or stages are less susceptible to repair without vascular repair or amputation of lower extremities. Compared to the Wagner grading, this superior in its outcomes. UTSA is now commonly used in different clinical trials and diabetic centres.[68] Although the UTSA system defines the potential for infection at each of the different ulcer depths, discovering the variations in species or the antibiotic choice required does not go further.[28] (Table 3)

Table 3: University of Texas classification.

Stages	Grades			
	0	**1**	**2**	**3**
A	Healed pre or post ulcerative lesion completely epithelialized	Superficial wound not involving bone tendon or capsule	Wound penetrating tendon and capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With ischemia and with infection	With ischemia and with infection	With ischemia and with infection	With ischemia and with infection

International working group classification

Another classification system provided by the International working group provides risk data that can predict individuals with diabetes at risk for foot problems.[69] The risk assessment instrument created by the International Diabetic Foot Working Group (IWGDF) was useful in assuring complications of the diabetic foot.[70] (Table 4)

Table 4: International working group on the diabetic foot.

Risk group 0	No neuropathy, no PVD
Risk group 1	Neuropathy, no-deformity PVD
Risk group 2	Neuropathy and deformity and or PVD
Risk group 3	History pathology

Diagnosis

Management of diabetic ulcers consisting of diagnosis and treating underlying cause of ulcers, wound care and prevention of ulcer recurrence. The cause can be determined through deep anamnesis and physical examination.[71]

History

Symptoms of peripheral neuropathy includes diabetes, hypesthesia, hyperesthesia, paresthesia, dysesthesia, radicular pain and anhidrosis.[72,73]

Physical examination

According to Stillman, the physical examination is divided into three sections[73] in patients with diabetic ulcers:

Examination of ulcers and general circumstances of the extremities

Diabetic ulcers tend to occur in some of the places that become the biggest heel loads, like the foot, the metatarsal head region on the hand, the prominent fingertips (on the first and second fingers). Ulcers can occur in malleolus because it is often traumatized in this region. Certain physical examiner anomalies include: hypertrophic callus, broken or damaged nail, hammer toes, and fissure.

Assessment of possible vascular insufficiency

Physical examination reveals that the peripheral pulse has disappeared or decreased below a certain amount. Certain symptoms consistent with atherosclerotic disease include iliac and femoral artery bruits, skin atrophy, leg hair loss, cyanosis of the toes ulceration, and ischemic necrosis, and pale feet when the foot is elevated for 1-2 minutes as high as the heart. Non-invasive vascular measures include transcutaneous oxygen levels, the Ankle Brachial Index (ABI) and the toe's systolic pressure Ankle brachial index is a non-invasive examination that uses the doppler tool to perform quickly. Pressure of the cuff mounted on the upper arm and pumped until the doppler could detect the pulse on the brachialis. Then the cuff is slowly released until the brachial pulse can be detected by the doppler. On the legs where the cuff is placed in the distal calf and the doppler is connected to the dorsalis pedis or posterior tibial artery, the same operation is performed. Ankle brachial index is determined by systolic brachial stress from the ankle.[24,62,74]

Assessment of possible peripheral neuropathy

Signs of peripheral neuropathy include loss of sensation of vibration and position sensation, loss of deep tendon reflex, tropical ulceration, foot drop, muscle atrophy, and hypertrophic callus formation, especially in areas of pressure, such as on the heel. The neurological condition can be evaluated using the monofilament Semmes-Weinsten to assess whether the patient still has a "protective sensation". The test shows abnormal results if the patient is unable to feel the monofilament touch when placed on the foot with enough pressure until the monofilament is bent. Another testing instrument is a 128 degree Celsius garputala, which can be used by inspecting the ankle and the first metatarsophalangeal joint to assess the sense of vibration. In the metabolic neuropathy, there is an intensity gradient and the most severe in the distal region. There is an intensity gradient in metabolic neuropathy and the most severe in the distal region. Thus, in patients who are unable to feel the wrist vibration when the toe rotation is removed from the toes to the wrist, intensity gradient is indicated due to metabolic neuropathy. Generally, the garputala's sensation on the fingers can't feel longer than 10 seconds after the patient can't feel the big toe vibrations. Most people with normal sensations show only the difference of less than 3 seconds between the sensations of the toes with the hand of the examiner.[24,73,74,75]

Laboratory examination

- Blood tests: Leukocytosis may be associated with an abscess or other foot infection. The presence of anemia inhibits wound healing. The presence of already existing arterial insufficiency causes pain in the rest.
- Metabolic profile: Blood glucose, glychemhemlobin and serum creatinine test largely determines the adequacy of glucose control and renal function.
- Non-invasive vascular laboratory examination: Pulse Volume Recording (PVR) or plethymosgraphy

Radiological examination

- A simple examination of the diabetic foot can demonstrate demineralization, Charcot joint and osteomyelitis presence.
- Computed tomographic (CT) scan or magnetic resonance imaging (MRI): although an experienced doctor can diagnose an abscess with a physical examination, a CT scan or MRI may be used to help diagnose an abscess if the physical examination is ambiguous.

- The efficacy of bone scanning is still questionable due to the large false positive and false negative results.
- Recent studies cite 99mTc-labeled ciprofloxacin as an indicator for osteomyelitis.
- Conventional arteriography: when conducting vascular or endovascular surgery, arteriography is necessary to demonstrate the nature and importance of atherosclerotic disease.

Alternatives to conventional angiography

- Magnetic Resonance Angiography (MRA): MRA is a substitute that can be used in elevated-risk patients or in patients allergic to contrast material. The comparison used was gadolinium chelates, which could cause 3 side effects in patients with renal failure: acute renal damage, pseudohipokalemia, and systemic nephrogenic fibrosis.
- Multidetector computed tomographic angiography (MDCT) stops arterial stabbing. Multidetector CT scans (16 or 64 channels) can enhance the quality of angiographic images at relatively high speeds by using intravenous contrast injection.
- Carbon dioxide angiography is an alternative to renal insufficiency patients, but it is not commonly used and also includes iodine contrast content as an additional carbon dioxide gas for a good image.
- In regular evaluation of occlusive peripheral arterial disease, simple radiography is not used. This is because a common indicator of atherosclerotic disease is not arterial calcification seen in plain radiographs. Arterial media layer calcification is not a diagnosis of atherosclerosis, and even intima layer calcification, which is a diagnosis of atherosclerosis, may not cause serious haemodynamic stenosis.

Management

DFU's primary care aim is to get wound healing as quickly as possible.[76, 77]

Blood sugar control

Glucose control in patients with DFU is the most significant metabolic factor. Indeed, inadequate blood sugar control is reported to be the primary cause of DFU.[6,78,79] The best indicator of long-term glucose control is the level of HbA1C. This test measures the mean concentration of blood sugar in peripheral circulation over a 90-d cycle of the average red blood cell. The higher the level of HbA1C, the more haemoglobin glycosylation occurs in red blood cells. Researches have shown that blood glucose levels > 11.1 mmol / L (equivalent to

> 310 mg / mL or > 12 HbA1C) are associated with reduced neutrophil function, including chemotaxis of leukocytes.[79] However, higher blood glucose levels are associated with a higher ability to suppress inflammatory responses and decrease the response of the host to an infection.[6] Pomposelli *et al*.[80] reported that on the first postoperative day, a single blood glucose level > 220 mg / dL was a strong predictor of postoperative infection (87.5%). In addition, the authors found that patients with blood glucose levels > 220 mg /dL had infection rates that were 2.7 times higher than patients with lower blood glucose levels (31.3% vs 11.5%, respectively).[80] It is also proposed that a 1% mean reduction in HbA1C was associated with a 25% reduction in micro-vascular complications, including neuropathy.[81] Research has found that poor control of glucose has exacerbated the development of Peripheral Arterial Disease (PAD). It has been shown that there is an increase of 25%-28% in the relative risk of PAD, which is a primary cause of DFU, for every 1% rise in HbA1C.[82]

To date, however, no RCT has been conducted to determine whether enhanced glucose regulation benefits after the formation of a foot ulcer.

Debridement

Debridement is an act of removal of non-living materials foreign bodies, and tissues that are hard to recover from injury.[83] Debridement to remove necrotic tissue and debris should be done on all chronic wounds.[84,85] Such intervention is achieved by removing the origin of abnormal injuries and wound edge tissue such as epidermal hyperkeratosis (callus) and necrotic dermal tissue, debris and bacterial elements which may inhibit wound heal. It has been found from several clinical trials that debridement plays a role in improving wound healing by developing granulation tissue.[86,87,88] Debridement is an important and decisive step in treating diabetic foot ulcers as an effort to prepare the wound bed by shifting the local environment or environment from a chronic wound to an acute wound to promote and improve the wound healing cycle.[89,90-92] There is a new wound bleeding at the time of debridement, so that the debridement action in diabetic foot ulcers can increase the levels of VEGF according to Frank *et al* 's[92] hypothesis. Frequent debriding of diabetic foot ulcers can increase the rate of wound healing, although there is insufficient evidence to support this view.[93] There are five forms of debriding: surgery, enzymatic, autolithics, mechanics, and biologics. Only surgical debridement in clinical trials has been shown to be successful. A quick debridement to remove both dead tissue and bone is surgical debridement. The aim of debridement is to make acute wound healing the chronic wound healing environment.

Enzymatic debridement with specially tailored proteolytic enzymes such as collagenase, papain / urea from papaya, fibrinolysis / DNAse, trypsin, combination streptokinase-streptodornase. For stable, moist and perfused ulcers, autolytic debridement occurs naturally. Mechanical debridging by dry-wet dressing, irrigation pressure, lavage and hydrotherapy. The larvae secrete a proteolytic enzyme that can dilute the necrotic tissue by using the sterile larvae of the Luciliasericatafly.[83, 63]

Offloading

For patients with lesions on the feet's soles, it takes offloading to shift the weight fulcrum away from the side of the ulcer by several methods or tools. The discharge is aimed at preventing tissue injury and promoting wound healing.[84,86] Offloading is a reduction in ulcer pressure, becoming one of the components of ulcer management for diabetes. Ulceration usually occurs with high pressure in the foot area. Bed rest is an excellent way to reduce pressure but the most effective method of offloading is the Total Contact Casting (TCC). TCC consists of specially formed casts to distribute the burden of the patient out of the region of ulcer. This approach allows the patient to walk during treatment and is effective in managing the occurrence of edema which may interfere with wound healing. While being difficult and long, TCC can reduce the pressure on the wound and is shown by 73-100 % healing. TCC's drawbacks include skill and time, plaster irritation can lead to new wounds, and daily wound diagnosis discomfort, increased use of Cam Walker, removable cast walker, regular examination of wound, change of dressing and early detection of infection. Some other approaches that can be done include bed rest, wheelchair use, specially designed walkers to shoes.[10,94]

Management of infection

Diabetic ulcers enable both bacterial entry and wound infection. A systemic method is needed for a proper assessment due to the high incidence rate of infection in diabetic ulcers. Infection diagnosis is based mainly on clinical conditions such as erythema, edema, pain, softness, warmth and discharge from pus.[95] It becomes very essential to determine the degree of infection. According to infectious diseases, the society of America splits the infection into three categories: (1) Mild infections: if erythema is < 2 cm; (2) Moderate infection: if erythema is > 2 cm; and (3) Severe infection: systemic infection.[95]

Diabetic ulcers are divided into two groups, namely

(1) Non-limbal threatens: cellulitis < 2 cm and does not extend to the bone or joints; and (2) Limb threatening: cellulitis > 2 cm and bone and joints, and systemic infection.[72] Research on the use of antibiotics as a diabetic ulcer therapy is still less, based solely on clinical experience. Antibiotic therapy should be based on the outcomes of bacterial culture and the toxicity of the antibiotic.[95] In non-limb-threatening infections are usually caused by staphylococcus and streptococcus. Mild and moderate infections may be treated for polyclinics by oral antibiotics, such as cephalexin, amoxilin-clavulanic, moxifloxin or clindamycin[71,73,95] In severe infections due to polymicrobial infection, such as staphylococcus, streptococcus, Enterobacteriaceae, pseudomonas, enterococcus and anaerobic bacteria, e.g. Bacteroides, Pepto cocci, Pepto streptococci. In sevee infections should be hospitalized, with antibiotics that that include gram positive and gram negative, and aerobic and anaerobic. The choice of intravenous antibiotics for serious infections includes imipenem-cilastatin, B-lactam B-lactamase (ampicillin-sulbactam and piperacilintazobactum) and broad-spectrum cephalosporin.[71, 72]

Dressing

Dressing is a substance that is used on the wound topically to secure the wound and help heal the wound. Dressing will be in direct contact with the wound and will be defined by plaster as a dressing barrier. There are many dressing categories: film, composite hydrogel, hydrocolloid, alginate, foam, and other absorptive dressing like negative pressure wound therapy (NPWT).[96, 97] In order to facilitate cell migration and prevent dry sores, a closed-clean-wound or granulated wound is primarily intended to provide a moist cure environment. The number and type of exudate in the wound depends on the dressing selection. Hydrogel dressing, film, composite is well used for cutting with a small amount of exudate. Hydrocolloids are used for wounds with exudate amounts and for wounds with exudate quantities alginate, foam and NPWT are commonly used. Until dressing, lesions should be debridged with large necrotic tissue.[97] Using an airtight dressing sponge on the wound, negative pressure wound healing and wound closure with a vacuum will be installed Negative pressure wound treatment may be used for wounds with significant lymph leaks and fistulas. The main mechanism of NPWT is to eliminate edema, NPWT removes interstitial fluid from the lymph or lymph, through the diffusion of interstitial oxygen into the cell. Negative pressure wound therapy also eliminates enzymes like collagenase and MMP that increase the levels of chronic wound.[96, 97]

Advanced therapies

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) has been useful in the treatment of serious non-healing cases of DFU resistant to other therapeutic methods.[98-101] HBOT includes administering 100% oxygen intermittently, usually in daily sessions.[102] During each session, patients breathed pure oxygen in an absolute atmosphere of 1.4-3.0 for 3 periods of 30 min (90 min) intercalated by 5 min intervals in a hyperbaric chamber.[98,103] RCTs have recorded positive impacts of HBOT in numerous researches today.[104-108] A latest double-blind RCT performed by Löndahl *et al*[108] showed a considerably enhanced result in the intervention group as the patients treated were more likely to heal within 12 mo [25.48 (52%) vs 12.42 (29%); P = 0.03]. Furthermore, in a systematic review, Kranke *et al*[109] found that HBOT therapy resulted in a considerably greater percentage of healed DFU compared to treatment without HBO (relative risk, 5.20; 95% CI:1.25-21.66; P= 0.02). However, no significant effects on amputation rates were found in the RCT evidence in another systematic review conducted by O'Reilly *et al*[110] and no difference was found between the HBOT group and the standard wound care group in the high quality studies. HBOT's exact mechanism remains poorly understood. Some studies indicated that HBOT improved wound tissue hypoxia, increased perfusion, decreased edema, decreased controlled inflammatory cytokines, and encouraged proliferation of fibroblasts, collagen manufacturing, and angiogenesis.[111-114] Furthermore, it was shown that HBOT stimulated the vasculogenic mobilization of stem cells from the bone marrow and recruited them to the skin wound.[113] Despite reports of enhanced healing rates and reduced amputation rates using HBOT, a controversial issue remains the adjuvant use of this technique in DFU. HBOT does not replace antibiotic therapy, local humid treatment or debridement of surgical wound. In addition, HBOT is accessible in only a minority of communities as it is costly [a complete course of treatment in the U.S. typically costs $50,000 (Medicare) to $200,000 (private pay)] and time consuming (an average of 60 total hours in the chamber).[5,6]

Electrical stimulation

Recent research has shown that electrical stimulation (ES) is an effective adjunctive therapy for healing DFU. A major work is currently underway to support the efficacy of ES for DFU healing.[115-118] In a randomized, double-blind, placebo-controlled trial study conducted by Peters *et al* [115] in 40 DFU patients, significant differences were identified in the rate of healed ulcers (65% in the control group vs 35%) at 12 wk. Based on the literature review, it is

proposed that specific deficiencies associated with deficient wound healing in DFU could be improved by ES.[115-119]

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is a non-invasive wound closure system using controlled, localized negative pressure to help cure acute and chronic wounds. This system uses latex-free and sterile polyurethane or polyvinyl alcohol foam dressing designed for each wound at the bedside and then covered with an adhesive drape to create an airtight seal. Most commonly, either continuously or in cycles, 80-125 mmHg of negative pressure is used. In the control unit, the fluid removed from the wound is stored in a container.[120,121] It appears that NPWT prevents edema and chronic exudate, decreases bacterial colonization, stimulates the formation of new blood vessels, increases cell proliferation, and improves wound oxygenation as a result of the mechanical force applied.[122,123] Numerous RCTs have promoted this approach as a safe and effective adjunctive tool in the treatment of DFU. Research have shown that wound healing with this method results in a higher proportion of healed wounds, a faster time for wound closure, a faster and more durable response of granulation tissue, and a possible trend towards a lower risk of second amputation than control treatment.[121,124-128] However, meta-analysis studies have shown that NPWT significantly reduces healing times and increases the number of healed wounds.[120,129,130]

Although NPWT evidence is encouraging in DFU patients, this approach does not substitute surgical wound debridement to improve blood circulation in all DFU patients. Evidence has shown that there must be no major infection or gangrene in the wound when NPWT is initiated.[120,130] In addition, RCTs reported significantly higher mean product expenses for NPWT-treated wounds compared to conventional therapy (moist gauze) for full thickness wounds requiring surgical closure.[131,132]

Bioengineered skin

Bio-engineered skin (BES) has been used as a new therapeutic approach of DFU treatment over the past decades.[133-136] This method replaces the degraded and destructive environment of extra cellular matrix (ECM) with the introduction of a new ground substance matrix with cellular components to start a new trajectory of healing.[137] There are currently three forms of BES approved in the U.S, products available for use in DFU, including Derma graft (Advanced Bio Healing Inc., La Jolla, CA), Apligraf (Organogenesis Inc., Canton, Mass), and more recently Oasis (Cook Biotech, West Lafayette, IN).[136,138] and multiple RCT

studies have shown their efficacy in DFU healing. BES product cells are grown in vitro and inserted into the scaffolds. In vitro incubation establishes the cells and enables accumulation in the scaffold of the cell-secreted ECM and growth factors. DFU healing is believed to accelerate the cells inside live cell scaffolds by actively secreting growth factors during the process of repair.[136,137] Furthermore; BES appears to be able to provide the cellular substratum and molecular components needed to accelerate wound healing and angiogenesis. Through the action of live human fibroblasts in the dermal elements, they act as biological dressings and as delivery systems for growth factors and ECM components.[134,135,139] Given the advantages of BES, DFU cannot be treated in isolation. A critical contributing factor that affects BES transplantation is peripheral ischemia, which is one of the pathological characteristics of DFU. Surgical revascularization and decompression as well as the preparation of wound bed are therefore considered essential prerequisites for BES applications. Therefore, this process requires infection control.[140,141] Consequently, the above-mentioned points that result in high long-term costs and cause significant concern for the use of this procedure.[142]

Growth factors

DFU has shown the effects of growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor, endothelial vascular growth factor, insulin-like growth factors (IGF1, IGF2), epidermal growth factor, and transformative growth factor b.[143] Among the aforementioned GFs, only recombinant human PDGF (rhPDGF) (Becaplermin or Regranex), a hydrogel containing 0.01% of PDGF-BB (rhPDGF-BB), showed improved healing levels relative to controls in a number of clinical trials[144-147] and showed enough efficacy of DFU repair to receive Food and Drug Administration (FDA) approval.[148] In a randomized placebo-controlled trial involving patients with full-thickness DFU (50 % vs. 35 %),[149] Becaplermin reported a 43 % increase in total closure vs. placebo gel. In another randomized placebo-controlled trial, Sibbald *et al*[150] presented that patients with infection-free chronic foot ulcers treated with the best clinical care and on-going 100µg/g Becaplermin gel applications had a significantly higher chance of 20 week 100% ulcer closure than patients receiving the best clinical care plus placebo (vehicle gel) alone. GFs have been shown to activate neutrophils, fibroblasts, monocytes and other components that form the cellular backbone of wound healing chemotaxis and mitogenesis,[144,151] Amid FDA approval and other evaluations, clinical use of Becaplermin remains limited due to its high cost[152] and unclear medical benefits[153,154] Several studies have shown that endogenous PDGF promotes

the infiltration of human melanoma tumor fibroblasts located in cells that are overexpressed at all stages of human growth.[136] Therefore, administering recombinant PDGF topically to promote cancer would be biologically feasible.

Patient education

Offer diabetic patients or their caretakers, both oral and written information on:

- The importance of blood glucose control.
- The modified cardiovascular risk factors such as diet, exercise, body weight, and cessation of smoking.
- The importance of foot care and counselling on basic foot care.
- Consider the patient's cultural practices and religious beliefs as well as social and family support.
- The patient's current risk of developing a foot problem.
- When to seek professional support and who to contact in foot emergencies.[155]

Footwear

Occlusive footwear causes sweating and can predispose to fungal infection.[156,157] especially in tropical countries. Ideally, footwear for individuals with diabetes must have a wide toe box, soft cushioned soles, extra depth to accommodate orthoses if essential, and laces or velcro for fitting and adjustment. A fresh couple of shoes can be worn until comfortable.[155]

Patient compliance with prescribed footwear is generally poor, especially at home where they are more active. Patients with forefoot or heel plantar ulcers may be provided offloading footwear to enable ulcer healing and prevent recurrence.

CONCLUSION

Diabetic foot ulcer is common in patients and frequently leads to lower limb amputation unless a prompt multidisciplinary approach is been taken for effective management of diabetic foot ulcer patient should be educated properly with appropriate blood glucose control wound debridement, offloading and advanced therapies which are used clinically. It could be expected that in near future more innovate techniques and concise treatment will hold a promise in proper management of DFU's.

Tips on foot care for people with diabetes[158]

- Check both feet daily, including the area between the toes. Ask a caregiver to do this if you are unable to.
- Wash the feet daily at room temperature with water, particularly between the toes, with careful drying.
- Using dry skin lubricating oils or creams, but not between the feet.
- Cut the nails straight through.
- Do not use a chemical agent or plaster to remove corn and calluses. They should not be taught at home and should be handled by trained personnel.
- Always wear shoe socks and check for foreign objects within your shoes before wearing them.
- Avoid barefoot walk at all times.
- Confirm a qualified healthcare provider to examine your feet frequently.
  Inform the healthcare provider at once if a blister, cut, scratch, or sore develops.

How can diabetic foot care services be organised in India?

Up to 415 million people worldwide have diabetes, with 75% living in low-and middle-income countries. About 70 million people in India have diabetes, and by 2040 the number is expected to grow to 125 million.[159] The National Institute for Health and Care Excellence guideline on diabetic foot mentions a three level classification for foot care: primary healthcare for preventive services and appropriate referral of diabetic foot; foot protection services at community level for podiatric care and management of simple foot problems; and multidisciplinary foot care services at tertiary level to handle complex foot problems.[160] Primary care doctors are not qualified in diabetic foot care in low-and middle-income countries, podiatry is emerging as a specialty, and multidisciplinary foot care services are available in a few tertiary care canters. We recommend training in diabetic foot care for primary care doctors, particularly in countries with a high diabetes burden.

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