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Diabetic foot ulcers: A devastating complication of diabetes mellitus continues non-stop in spite of new medical treatment modalities

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Abstract

Diabetic foot ulcer is a devastating complication of diabetes mellitus and significant cause of mortality and morbidity all over the world and can be complex and costly. The development of foot ulcer in a diabetic patient has been estimated to be 19%-34% through their lifetime. The pathophysiology of diabetic foot ulcer consist of neuropathy, trauma and, in many patients, additional peripheral arterial disease. In particular, diabetic neuropathy leads to foot deformity, callus formation and insensitivity to trauma or pressure. The standard algorithms in diabetic foot ulcer management include firstly assessing the ulcer grade classification, surgical debridement, dressing to facilitate wound healing, off-loading, vascular assessment (status and presence of a chance for interventional vascular correction), infection and glycemic control. Although especially surgical procedures are sometimes inevitable, they are poor predictive factors for the prognosis of diabetic foot ulcer. Different novel treatment modalities such as nonsurgical debridement agents, oxygen therapies, and negative pressure wound therapy, topical drugs, cellular bioproducts, human growth factors, energy-based therapies and systematic therapies have been available for patients with diabetic foot ulcer. However it is uncertain whether they are effective in terms of promoting wound healing related with limited number of randomized controlled trials. This review aims at evaluating diabetic foot ulcer with all aspects. We will also focus conventional and novel adjunctive therapy in diabetic foot management.

Key Words: Diabetic foot ulcer; Peripheric artery disease; Macrovascular complications; Neuropathy; Wagner classification; Intralesionar growth factor treatment

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Core Tip: Diabetic foot ulcers (DFU) are one of the most common problems and devastating complications of diabetes and affects 15% of all diabetic patients and results in significant morbidity, mortality and financial burdens. The management of DFU is usually complex and challenge to clinicians in clinical practice. This review article aims at summarizing etiopathogenesis and classification of DFUs. It also highlights novel adjunctive treatment modalities as well as conventional management.

INTRODUCTION

Diabetic foot ulcers (DFU) are common clinical problems and devastating complications of diabetes and affect 15% of all diabetic patients and results in significant morbidity, mortality and financial burdens[1]. Five-year risk of mortality of at 5 years for a patient with diabetic foot ulcer is 2.5 times higher than the risk for a patient who does not have diabetic foot ulcer[2]. Approximately 20% of moderate or severe DFU could cause some level of amputation. Moreover, 74% of them also have risk renal replacement therapy at 2 years[3]. This high mortality rate is also related with coexisting comorbidities such as cardiovascular or cerebrovascular diseases.

The pathophysiology of diabetic foot ulcer is based on a triad of neuropathy, peripheral arterial disease and concomitant secondary bacterial infection. Peripheral neuropathy could lead to intrinsic muscle atrophy and functional anatomical changes in the foot[4]. Eventually, progressive secondary foot infection penetrating deep facia, tendons and joints could develop with repetitive inattention trauma. Infection could play a significant role for half of major lower limb extremity amputations. Recent

studies indicate some risk factors with the development of diabetic foot ulcer. These are as follows: Longer than 10 years of duration of diabetes, male gender, older patients, presence of comorbidities including nephropathy, neuropathy, peripheral vascular disease and history of foot ulceration[5-7].

The management of DFU is usually complex and challenge to clinicians in clinical practice. Costs of diabetic foot ulcerations have been increased the treatment cost of many common cancers. Estimated costs of diabetic foot ulcer are greater than 1 billion in both developed and developing countries. Therefore, foot ulcers should be treated immediately by a multidisciplinary expert team for optimal outcomes. The treatment of DFU requires a immediate decision and systematic approach that comprises of maintaining arterial blood flow, treating of the infection appropriately and removing the pressure from the wound[8]. In addition, several adjuvant therapies are becoming a popular form of diabetic foot treatment. During the past 10 years, there has been an increasing amount of novel, basic science-based approaches and developments for adjuvant therapies including wound dressing, hyperbaric oxygen therapy or growth factor formulations for efficient local delivery[9-11]. None of them had definitive results that improved wound healing and these approaches still need clinical validation.

The review highlights novel adjunctive treatment modalities as well as conventional management.

PATHOPHYSIOLOGY

Diabetic foot ulcer is a serious result of risk factors including neuropathy, peripheral arterial disease and secondary infection. Mainly peripheral neuropathy could play a major role by producing intrinsic muscle atrophy and consequently leading to biomechanical anatomical changes on the feet such as hammer-toe formation, pes-planus, pes-cavus, which lead to high-pressure zones of the foot[12,13] (Figure 1).

Diabetic neuropathy and foot ulcer

The diabetic neuropathy has multiple manifestations within the diabetic foot because it comprises sensory, motor and autonomic fibers. Majority of the patients with diabetes (66%) face peripheral neuropathy in the lower extremities[13]. Especially distal sensory neuropathy, the most type seen of all diabetic neuropathies, is a major risk factor for DFU but it is extremely variable, as it ranges from severely painful symptoms to a completely painless variety that may present with an insensitive foot ulcer[14]. Diabetic peripheral neuropathy mainly affects lower legs and the feet as a stocking-glowing distribution and it could cause the loss of the Achilles reflex which can be the first sign of these changes. The anatomy of the foot arch could change with the atrophy of the lumbricals and interosseus muscles and a relative increase in the extensor tendon forces called as "claw" deformity in the toes[15]. On the other hand, the onset of sensory neuropathy can manifest as loss of proprioception, pressure sensation, vibratory perception and impaired gait[16]. Sensory neuropathy usually progresses gradually with the insidious appearance of symptoms that may be intermittent in the early stage. C-type fiber which is a responsible for the sensorial transmission result in inappropriate reaction to a painful stimuli[17]. Ulceration and infection could occur with repetitive trauma and decreased sensation and proprioception could also predispose skin injury by producing atrophy and dislocation of protective plantar fat pads. Moreover sudomotor dysfunction could developed with diabetic autonomous neuropathy and it is also associated with foot ulceration due to dry skin and itching[18]. Several methods are developed to evaluate the sudomotor function. They are thermoregulatory sweat testing (TST), quantitative sudomotor axon reflex (QSART), quantitative direct and indirect reflex test (QDIRT) and indicator plaster[19-21]. Among of them, indicator plaster represents a rapid simple method based on color change from blue to pink at the plantar foot region.

Since defining neuropathic symptoms could be difficult due to symptoms' fluctuation, a diagnosis of neuropathy may be difficult. Small fiber function can be determined by pinprick and a cold or warm thermal stimulus to the distal sensation. The proximal sensory abnormality could be determined by moving the individual test

paradigms proximally. Positive stimulus (allodynia and hypersensitivity) for diabetic neuropathy, can be showed by measuring the intensity or area of these phenomena. Negative symptoms in diabetic neuropathy are also numbness, no sensation, poor balance or muscle weakness. Clinical examination in these patients can include quantitative sensory testing (QST) to asses this sensory stimuli and also provide the advantage of directly assessing the degree of sensory loss in the foot. Some of the more commonly used techniques are "Semmes-Weinstein Monofilaments", ''Threshold of Thermal and Cooling '', "Perception of Vibration", and "Computer-Assisted Sensory Examination"[22-24].

Semmes-Weinstein Monofilament includes nylon filaments which have variable diameters and is one of the clinical tests that measure the response to a touching sensation of the monofilaments using a numerical quality. Inability to perceive pressure of 10-g (5.07) by the monofilament has been shown in subjects who are at risk for neuropathic foot ulceration (Figure 2). This is a very easy and applicable examination in busy outpatient clinics and reveals diabetic foot ulcer risk. It is recommended it to all practitioners[25].

Perception of vibration, which is called deep sensation impairment, is usually one of the earliest signs of peripheral diabetic neuropathy. 128 Hz tuning forks are generally used in general practice; these determine the perception of vibration through the application on distal bony prominence of the great toe bilaterally and other bony prominences such as medial malleolus. Sensitivity of tuning fork is approximately 53% and it is less predictive for the development of foot ulceration compared to using monofilament test[26].

Although electrophysiology is not required for clinical diabetic neuropathy evaluation, but it provide quantitatively assessing large fiber involvement in diabetic neuropathy. While these QSTs are convenient techniques in daily clinical practice, simple clinical instruments including Michigan Neuropathy Screening Instrument (MNSI) and Simplified Neuropathy Disability Score (NDS) can be used to assess

neurologic deficits. Now these scoring systems become using in a number of ongoing trials in new therapies for diabetic neuropathy[27,28].

Although it is not the main topic of this review, briefly neuropathy management is done symptomatically and current therapeutic agents which are used, including tricyclic antidepressants, Serotonin and Noradrenalin reuptake inhibitors and anticonvulsants have efficacy in diabetic neuropathy[29]. Among these new anticonvulsants pregabalin and gabapentin have been shown to be more convenient in the treatment of painful syndromes in recent articles[30].

Callus, deformity and plantar shear stress

Calluses have been defined as hyperkeratosis caused by excessive mechanical loading. Calluses increase pressure of plantar area and development the risk of diabetic foot ulcers[31]. Significant risk factors for callus deformity in patients with diabetic neuropathy are follow as foot deformity, limited joint mobility, repetitive stress of walking and ill-fitting shoes[32]. Calluses are frequently developed under bony prominence including metatarsal head. Proprioceptive loss due to sensory neuropathy and metatarsal heads leads to increased pressure and load under the diabetic foot. It has been reported that callus deformity may be related with relative risk of 11 for ulcer development (Figure 3). As a result of, removal of plantar callus is associated with reduced plantar pressure, thereby reduced foot ulcer risk.

Charcot neuroarthropathy

Charcot neuroarthropathy (CN) have been determined chronic and destructive disease of the bone structure and joints in patients with neuropathy. The precise incidence of CN in persons has previously been estimated to be between 0.1%-0.4%[32]. Etiopathogenesis of CN is complex and based on varied degrees of neuropathy. Typical clinical symptom is characterized by painful or painless bone and join destruction in limbs that have lost sensory innervation. Although the clinical management of CN have many clinical challenges; it is generally characterized with asymptomatic nature such as

ankle sprain, cellulitis, thrombosis[33]. Diagnosis of CN is based on primarily on thorough history and physical examination, with corroborating laboratory investigations and diagnostic imaging. Modified eichenholtz classification is commonly used for description in the clinical stage[34] (Figure 4). According to this classification; Stage 0 is mild inflammation, soft tissue edema and normal X-ray; stage 1 is severe inflammation, abnormal X rays with microfractures; stage 2 with coalescence, end of bone resorption and stage 3 with definitive bone remodeling with chronic CN.

Initial weight-bearing radiography can show demineralization, fragmentation, joint dislocation, osseous debris and joint space obliteration[35]. But routine radiography gives limited information about the differentiation of CN from osteomyelitis. Imaging techniques including magnetic resonance imaging (MRI) or PET/CT scans highlight the inadequacies of clinical examination and radiographs in assessing the CN stage[36]. Orthopedic surgery is often required to correct severe foot deformities when conservative measures including physiotherapy are not effective (Figure 5).

Peripheral vascular disease

Peripheral vascular disease is characterized as chronic arterial occlusive disease of the lower extremities and varies in severity. Patients with peripheral arterial disease have usually intermittent claudication, rest pain and tissue loss with or without gangrene[37]. Rest pain is shown in these patients and related with chronic sensory nerve ischemia. Resting pain emerges as a diffuse burning or aching pain in the fore foot[38]. Intermittent claudication and rest pain are the clue to diagnose, though they can lack symptoms or can be difficult to be attributed exclusively to peripheral vascular disease. Any worsening of walking quality or speed should be taken into account as well as fatigue, pain, cramps, discomfort or burns in buttocks, thighs or feet. The extent of ischemia and symptoms are related with location vascular lesion as well as the developing of collateral circulation[39]. Generally patients with aorto-iliac disease have buttock and thigh pain, and femoral disease causes calf discomfort. Tibio-peroneal disease generally

does not have claudication, although some patients will complain of foot pain or numbness while walking.

Pulse palpation (distal pedis, posterior tibial, posterior tibial, popliteal and femoral arteries), which can be simple, cheap and comfortable clinical examination, should be performed on all diabetic patients during the follow-up examination. Ankle-brachial index (ABI) has emerged as a relatively non-invasive tool for the diagnosis of peripheral arterial disease[40]. The measurement of ABI (ratio of systolic blood pressure on the ankle to the systolic blood pressure in the upper arm) is normal in the 1.0-1.4 range, obviously pathologic under 0.9. An ABI over than 1.4 is also considered as abnormal, reflecting calcified and stiffed arteries. The doppler ultrasound exam, computed tomography angiography are often used as non-invasive tests[41]. Intra-arterial digital subtraction angiography is defined as the gold standard for arterial imaging because of its high spatial resolution. It has the advantage of allowing endovascular therapy during the same procedure and it is also extremely accurate for the smaller vessels of the ankle and the foot. But it has a disadvantage for patients with renal insufficiency [glomerular filtration rate (GFR) < 35 mL/min/1.73 m^2][42].

Infection and osteomyelitis

Infection in ulcerated diabetic foot is a primary cause of morbidity and mortality. It is well known that diabetic patients are prone to infectious diseases because of the diminished host defenses, including inadequacy in leukocyte capacity and morphologic alterations to macrophage, elevation of proinflammatory cytokines and impairment of diabetic polymorph-nuclear cell functions (chemotaxis, phagocytosis, killing)[43,44]. Many organisms can cause diabetic foot infection, but gram positive cocci, especially *staphylococci* (*S. Aureus*) are the most common cause pathogens[45]. Peripheral neuropathy, angiopathy and a lack of attention to foot hygiene, using poorly fitting footwear are the major factors in the development of infection. Abrasions, rashes, loss of skin integrity due to fungal infection can be facilitating factors for diabetic foot infection. Approximately 60% of foot infections starts in webbed spaces and 30% in

nails, while 10% are secondary punctures[46]. Ulcers > 60 mm^2 in size, purulent discharge from sinus tract, presence of sausage toe, Erythrocyte Sedimentation Rate (ESR) > 70 mm/h suggest the presence of underlying osteomyelitis[47]. Osteomyelitis could be able to occur after the spread of superficial infection of the soft tissue on the adjacent bone or marrow. Although numerous expensive radiology techniques are available to diagnose osteomyelitis, specific clinical signs of inflammation (swelling, erythema, warmth, tenderness, pain or induration) and the use of simple metal probes can often be used to make clinical diagnoses. In initial clinical visit; plain radiographs should be obtained to determine the extent of osseous erosion, as well as to assess anatomy for surgical planning. Further scanning tests including MRI, bone scans could be performed for patients with neuropathic osteoarthropathy or multifocal disease[48-50].

CLASSIFICATIONS OF FOOT ULCERS

Identification and classification of patients with diabetic foot ulcer should be classified whether the hospitalization, intravenous (IV) broad spectrum antibiotics or surgical consultations will require or not. An accurate defining of ulcer characteristics such as size, depth, appearance and location allows for the mapping of progress during management of diabetic foot ulcer. There have been several classification systems that have been broadly externally validated for ulcer healing and lower extremity amputation and they are Meggitt-Wagner, University of Texas, Infectious Disease Society of America (IDSA), Perfusion, extent, depth, ischemia, sensation (PEDIS), SINBAD, Wound, Ischemia and foot infection (WIFI) classification[51-53].

Wagner classification was the first announced classification system, however it is not well validated and does not distinguish well between ulcer types for the main purpose of classification. This system consists of 6 different groups: 0, intact skin; 1, superficial ulcer; 2, ulcer reaching to tendons, joints, bones; 3, deep ulcer with abscess; osteomyelitis; 4, local gangrene; and 5, gangrene of the entire foot. It presents vascular perfusion only when gangrenous changes appear and infection when osteomyelitis is present (Table 1).

The university of Texas classification is well validated but it does not indicate neuropathy or depth of the ulcer area, which is considered to be one of the main determinants of the ulcer healing (Table 2). IDSA was reported as a guideline and diabetic foot is subclassified into the categories of uninfected, mild (restrictive involvement of only skin and subcutaneous tissue), moderate (more extensive) and severe (systemic signs of infection).

PEDIS classification was based on the 5 features of the wound and it helps clinicians assess risk or prognosis for a person with diabetes and active foot ulcer. In addition, it was used for a clinical audit study in 14 European countries[54].

SINBAD classification system matches each composing variable such as area, depth, infection, neuropathy to a score (ranging from 0-6). This classification system has some benefits such as simple, quick to use and not required specialist equipment[55].

WIFI include three prognostic factors that affect clinical management. These factors indicate wounds that are graded from 0 to 3, ischemia graded toe pressure index and infection which is based on IDSA classification. WIFI threatened limb classification has been shown to correlate well with a risk of major amputation but it is not enough make acute decisions about the treatment only by itself due to more confounding factors (Table 3).

Up to date there has been several classification systems but which classification to use is still controversial. Physicians who treat patients with DFU are concerned about which classification is recommended. They are still discussing the usefulness of these classifications and effects of such classifications on diagnosis or treatment remain unknown. Although there are some limitations in case of prognostic accuracy of Wagner Classification, this classification remains the most commonly utilized system in health care today.

MANAGEMENT OF DIABETIC FOOT ULCER

The main principle of management of diabetic foot ulcer is to evaluate wound appearance (extent, size, depth, presence of infection, wound duration) in detail.

Clinicians should inspect the extent of tissue destruction and possible bone and joint involvement. After evaluating wound appearance, another major decision is whether the patient can be initially treated as an outpatient or needs hospitalization. Early superficial ulcer (< 2 cm) without systemic toxicity may be treated at home. If the patient has deep gangrenous ulcer with infected or systemic symptoms or needs surgical treatment, hospitalization is advised.

Since diabetic ulcer healing depends on multiple factors, it should be evaluated by a multidisciplinary expert team. The treatment includes conservative and surgical interventions and there are some fundamental steps of diabetic foot management such as; surgical debridement, dressing, wound off-loading, vascular assessment, control of infection, glycemic control and adjuvant therapies[56-59] (Table 4).

Surgical debridement

Debridement is a principal treatment of local wound healing and it involves removing hyperkeratotic epidermis (callus), necrotic dermal tissue, foreign debris, and bacterial elements from a wound bed. Debridement includes numerous forms such as mechanical, autolytic, enzymatic and sharp[60,61]. Sharp debridement is commonly more common to use, and it includes 2 forms such as; clinic based debridement and surgery based excisional debridement. A combination of debridement methods could help to remove devitalized tissue and provide a nidus for bacterial proliferation act as physical barrier for antibiotics. Debridement is the most important step of the wound healing. If necessary, it should be performed in every clinic visit by clinicians.

Dressings

After the adequate debridement period, soft tissue defect requires dressing materials for closure and/or coverage of wound area. Dressing with adequate biomaterials could provide wound healing processes and protect from contamination. Naturel skin is considered perfect wound dressing and therefore ideal wound dressing should try to mimic its properties. Since recent studies highlighted the role of wound environment,

dressing also should be biocompatible and not provoke any allergic or immune response reaction and should be easily removed[62,63]. Alginate and collagen-alginate products, carboxymethylcellulose dressings, topical phenytoin, hydrogels are types of dressings which are available[64,65]. But there have been still some questions to support the choice of any dressings or to promote healing of ulcer.

Wound off-loading

Plantar shear stress and vertical plantar pressure are major causative factor in the development and poor healing of diabetic foot ulcer. Removal of pressure and/or redistribution of weight bearing an increased area of the foot can be achieved through off-loading strategies. Total contact casts and removable walkers are used for off-loading the diabetic foot[66]. Various therapeutic off-loading devices such as rock or bottom outsoles, custom-made insoles, some shoe inserts (*e.g.*, metatarsal pads and medial arch supports) may reduce fore foot peak pressure[67,68]. Recently, International working group[69] on the diabetic foot suggest these recommendations follow as: (1) Removal pressure on ulcers is one of the main part of the treatment plan; (2) non-removable walkers are the preferred treatment; and (3) forefoot off-loading shoes or cast shoes may be used when above-the-ankle devices are contraindicated.

Vascular assessment

Revascularization of critically ischemic legs results in increased area perfusion after the procedure which in turn associated with a further reduced amputation rate. Arterial revascularization can be performed through open procedures such as a bypass or, in many cases, an endovascular recanalization followed by PTA (percutaneous transluminal angioplasty) or an endovascular recanalization followed by with or without adjunctive stenting[70]. Overall the aim of vascular reconstruction is to restore direct pulsatile flow at least one or more arterial structures, preferably feeding the wound.

Control of infection

The diagnosis of infection is based on presence of parameters of inflammation and should always be classified according to preferred classification method. Antibiotic therapy is based on possible pathogens, presence of vascular disease and the extent of foot infection. Hospitalization with parenteral antibiotic treatment is recommended when the infection penetrates to the deep fascia. Patients with chronic ulcer, prior antibiotic treatment and recurring infection should be assumed to have methicillin-resistant *Staphylococcus Aureus* infection[71]. The spectrum can be broadened to cover Gram-negative aerobes in chronic infections. If the patient had superficial ulcer without infection, empiric antibiotic treatment therapy is not recommended[72]. Oral therapy including Trimethoprim/Sulfamethoxazole or Amoxicilline/Clavulanic acid plus linezolid is recommended to the patients with superficial ulcer and presence of pedal pulses. Parenteral therapy such as Vancomycin or daptomycin plus piperacillin/tazobactam or imipenem cilastatin or meropenem has been recommended to patients with systemic inflammation or ulcer/gangrene with penetration of deep fascia[73,74]. In addition, in order to avoid antibacterial resistance or other adverse outcome of therapy, it is the best approach to be followed.

Glycemic control

In hospitalized patients, intensive insulin treatment should be administered to patients with foot ulcer for better glycemic control. The evidence of glycemic control can accelerate the healing of foot ulcers and reduce the incidence of ulceration and amputation. Studies have shown that increased blood glucose level is correlated with decreased neutrophil function and suppression of inflammatory response[75-77]. Although there are limited Randomized Control Trials (RCT) which determine whether glycemic control improves wound healing better. In meta-analyses which included 10.897 patients without known history of peripheral artery disease, it has been that reported intensive glycemic control was associated with a statistically significant decrease in risk of amputation of diabetic foot[78].

Adjuvant therapies

New treatment modalities have been developed since 2002. There are advanced wound therapy methods. In addition to conventional therapy, several types of treatment modalities are available available such as negative pressure wound therapy, which is also known as vacuum assisted closure (VAC), synthetic skin grafts, non-surgical debridement agents, topical growth factors, electrical stimulation and hyperbaric oxygen chambers[79-85] (Table 5). Each has its own merits but economic constraints and patient compliance should be kept in mind.

Negative pressure wound therapy

Pressure wound therapy (VAC) was first declared and used in clinical practice by the German physician Fleischmann in 1993[79]. It has remarkable effect on wound drainage, also enhancing perfusion. VAC could be used for acute and chronic diabetic foot ulcer and it promotes the growth of granulation tissue (Figure 6). It can be helpful in the postoperative management of diabetic foot ulcer. According to Wound Healing Society and European Wound Management[80]: (1) Wound infection should be well controlled after the debridement; (2) the risk of bleeding is well controlled; there is no active bleeding or exposed vascular damage on the wound or no risk of coagulation dysfunction; and (3) the risk of ischemia is treated and well controlled (ABI ranges from 0.9 to 1.3), VAC therapy is recommended with class 1 evidence. After 1-2 rounds of VAC therapy, a comprehensive evaluation should be performed for an effective evaluation. It is recommended to continue VAC, If there is growth of new granulation tissue on the wound surface with surrounding epithelization, If infection is aggravated, it should be stopped immediately. In recent years, VAC treatment has been used extensively for diabetic foot ulcer and studies have shown that it has certain advantages in preventing and controlling wound infections.

Synthetic skin grafts

Skin substitutes are classified into three groups based on plasticity of preparation procedure and composition of the substitutes. Class 1 skin layer include cultured epidermal equivalent which are formed of single-layered materials; Class 2 layer include dermal components from processed skin or fabricated matrix protein; Class 3 layer also consist of dermal and epidermal components and skin grafts (allograft, xenograft)[82] lass 3 layer is more popular and common to use. Although there are limited studies, wound healing by adding extracellular matrix can be promoted by using these agents.

Non-surgical debridement agents

Although sharp debridement can play a major role in wound healing, various techniques such as autolytic debridement with hydrogels, enzymatic debridement, maggot and larval debridement, hydrotherapy are available[83,84]. But recent studies did not provide sufficient evidence to use one approach over other methods.

Hyperbaric oxygen chamber

Administration of 100% O_2 have some beneficial effect on wound healing. It causes increased blood and oxygen content in hypoxic tissue and it has also antimicrobial activity due to enhanced mobility and bacteriophagic activity of leukocytes[85]. Studies show that hyperbaric oxygen stimulates angiogenesis and increased fibroblast proliferation, collagen production. Some authors suggested there are no definite results which display an improvement in DFU. There is large uncertainty associated with the evaluation of the cost-effectiveness hyperbaric oxygen therapies. Up to date; there have been 7 RCTS and these studies showed that hyperbaric oxygen chambers are beneficial for preventing amputation and promoting complete healing in patients with Wagner grade 3 or greater diabetic foot ulcer[86,87]. In patients with Wagner grade 2 or lower diabetic foot ulcer, there is inadequate evidence to justify the use of hyperbaric oxygen therapy as an adjuvant treatment. The most common adverse events associated with

hyperbaric oxygen therapy are barotraumatic otitis, the inability equalize middle ear pressure and worsening of cataracts.

Topical growth factor

Epidermal growth factor (EGF), ascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) are polypeptide growth factors that have significant effects on tissue repair processes. These growth factors (EGF, VEGF, PDGF, FGF) are released by platelets and activated macrophage that are required for normal wound repair[88,89]. Growth factors which are used topically was reported to reduce the incidence of lower limb amputation. Using of growth factors is essential to provide angiogenesis, enzyme production, cell migration and proliferation.

PDGF is a crucial factor in wound healing and serves as a chemo attractant for the migration of fibroblasts, neutrophils to the site of injury. It is the first recombinant growth factor approved for topical application of wound healing. Fewer RCTs evaluated the effectiveness of PDGF and all studies applied the topical gel with different concentrations[90,91]. Majority of them did not find significant healing improvements compared to the standard wound care.

FGF acts as a balance factor in the body and is important for tissue maintenance, repair, regeneration and metabolism. FGF is a stronger angiogenesis factor than PDGF and VEGF. And FGFs stimulate angiogenesis and proliferation of fibroblasts, forming granulation tissue. FGF has some limitations for the treatment of DFU wound healing, since growth factors generally have a short half-life and require repeated administrations[92].

EGF is wound modulator that is involved in cell migration and proliferation. Injecting EGF deep into the wound bottom and contours encourages a more effective pharmacodynamic response in terms of granulation tissue growth and wound closure[93,94]. EGF is perhaps the most widely used method in diabetic foot wound

therapy but the results of studies are controversial or neutral. But our clinical experiences have been promising for healing foot ulcer (Figure 7).

Low level laser therapy

Low level laser therapy (LLLT) is a novel adjunctive therapy and is known to supply direct biostimulative light energy to body cells. This energy could lead to stimulate molecules and atom of cells but does not cause significant increase in tissue heat. Although different laser wavelengths have different depth of penetration of tissue, but red laser has a deeper penetration that the other such as violet, blue, green, yellow[95]. LLLT which can be considered as a possible new treatment option for the diabetic foot, has a various effect on wound healing by cellular migration or penetration[96]. Otherwise clinical trials using human models do not provide sufficient evidence to establish the uselfulness and practical method in wound care regimes.

Although these newly adjunctive treatments have some benefits, they are costly and should be reserved for ulcers that fail to respond to standard treatments. Adjunctive treatment modalities should be considered as an addition to good wound care which must always include adequate off-loading and debridement therapy. Current evidence points towards VAC therapy and local stem cell application as an effective treatment than the other adjunctive modalities for diabetic foot healing. There is a need for well-designed blinded randomized controlled trials to determine the true efficacy of these interventions and to develop evidence- based practice guidelines.

PREVENTION OF FOOT ULCERATION

Diabetic foot ulcerations are a devastating complication of diabetes mellitus. The mainstay of diabetic foot intervention is prevention. Preventative strategies in the form of education and regular foot assessments for peripheral vascular diseases and neuropathy along with risk stratification form the basis of the management of diabetic foot disease. Recently published guidelines highlight risk stratification for the assessment developing risk for diabetic foot ulcer or risk of future amputation[57,97].

Very low risk: No loss of protective sensation and no peripheral artery disease (PAD); Low risk: Loss of protective sensation or PAD or presence of callus formation alone; Moderate risk: Loss of protective sensation and PAD or presence of foot deformity; High risk: History of previous ulceration or previous amputation or renal replacement therapy or neuropathy and non-critical ischemia, neuropathy with callus.

According to IWGDF prevention guidelines, it is recommended to examine a person who has a low risk of foot ulceration annually for signs or symptoms of loss of protective sensation and peripheral artery disease. Patients with moderate or high risk should be screened every 3-6 mo. A person's risk status may change over time, thus requiring continual monitoring. Patients who have a risk of foot ulceration should be informed about controlling the whole surface of boot feet and the inside of shoes daily. Patients with moderate or high risk should be warned about wearing proper footwear to reduce plantar pressure. If there is a pre-ulcerative sign such as callus, appropriate treatment should be performed. Achilles tendon lengthening, joint arthroplasty, single or pan metatarsal head resection may be considered for patients who cannot heal with non-surgical therapy.

If the preventative treatment modalities are carried out for patients with diabetes, the global patient and economic burden of diabetic foot disease can be considerably reduced. Decreasing the risk of ulceration also reduces the risk of infection, hospitalization and lower extremity amputation in these patients.

CONCLUSION

DFU constitute a substantial burden for all over the world. Optimized therapy requires a collective refocusing on prevention and reallocation of resources from simply healing active ulcers. Multidisciplinary expert team are necessary for management of complex diabetic foot ulcer and therefore multidisciplinary approach to patient care reduces the risk of amputation in patient with DFUs. A combination of care from vascular, cardiovascular, infectious disease and endocrinology disciplines as well as podiatrists and wound care specialists provides a full range of care for the patient with DFU.

Conventional therapies including debridement, off-loading, vascular assessment, control of infection are principal treatment modalities. Otherwise; better outcomes could be obtained when the conventional treatment are combined with additional treatment in suitable patient.

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