Clinical Research on Foot & Ankle
ISSN: 2329-910X

Singh et al., Clin Res Foot Ankle 2013, 1:3
DOI: 10.4172/2329-910X.1000120

Review Artic Open Access

Diabetic Foot Ulcer – Diagnosis and Management

Simerjit Singh*, Dinker R Pai and Chew Yuhhui

Department of Orthopaedics, Melaka Manipal Medical College, Jalan Batu Hampar, Bukit Baru, Melaka, Malaysia

Abstract

Diabetes Mellitus is known to have many complications and one of the most distressing is diabetic foot ulcer which affects 15% of people with diabetes. It puts enormous financial burden on the patient and the health care services, even though it is preventable. Diabetic foot ulcer is characterized by a classical triad of neuropathy, ischemia, and infection. Each of these has a multifactorial aetiopathogenesis. These factors are compounded by mechanical stress created by foot deformities. The most commonly used classification systems are the Wagner-Ulcer Classification system and the University of Texas Wound Classification. These classifications help to predict the outcome of this condition. Prevention of this condition is paramount to prevent long term morbidity and sometimes mortality. This can be achieved by patient self-awareness and emphasis on regular foot examinations during follow-up. Care of the diabetic foot should be multidisciplinary. Debridement, dressings and offloading are the pillars of local management. Simultaneous glycemic and infection control is also essential. Amputations are usually the treatment of last resort but occasionally can be considered early to allow for faster mobilization and rehabilitation. Causative factors like peripheral vasculopathy and neuropathy must also be appropriately treated.

Keywords: Diabetes mellitus; Vasculopathy; Amputations; Multifactorial aetiopathogenesis; Neuropathy; Ischemia; Infection

Introduction

Diabetes mellitus (DM) is a serious and complex disease affecting almost all the vital organs in the body. About 347 million people in the world are diagnosed with DM [1] and majority of them are due to DM type 2 [2]. In recent years, studies have substantiated the relationship of sugar sweetened beverages and cardiovascular diseases, type 2 DM and long term weight gain [3]. The incidence of DM is on the rise and it has been predicted that it will increase by a double by the year 2030 [4]. DM is known to have many complications and one of the most distressing is Diabetic Foot Ulcer (DFU) which affects 15% of people with diabetes [5]. The incidence and importance of this complication is highlighted by the fact that papers on diabetic foot in Pub-Med have increased from 0.7% in the 1980-88 to 2.6% in 1998-2004 [6]. DFU is prone to infections, chronicity and recurrence which eventually affect the mental health of patients [7]. A benign looking ulcer in a patient with diabetes often ends up in amputation. A study in the United States reported that 38% of all the amputations were associated with DM [8]. This can lead to severe morbidity and mortality. Therefore DFU puts enormous financial burden on the patient and the health care services, even though it is preventable [9]. The successful DFU management strategies involve intensive prevention, early assessment and aggressive treatment by a multi-disciplinary team of experts. The aim of this review is to discuss the current diagnostic and management options for diabetic foot ulcer.

Aetiopathogenesis

DFU is characterized by a classical triad of neuropathy, ischemia, and infection [5]. Due to the impaired metabolic mechanisms in DM, there is an increased risk of infection and poor wound healing due to a series of mechanisms which include decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis [10]. Thus, the feet are predisposed to peripheral vascular disease, damage of peripheral nerves, deformities, ulcerations and gangrene.

Neuropathy

Neuropathy causes more than 60% of the foot ulcers [11] and affects patients with both type 1 and type 2 DM. Rise in blood glucose levels leads to increased enzyme production such as aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose into sorbitol and fructose. As these sugar products accumulate, the synthesis of nerve cell myoinositol is decreased, affecting nerve conduction [11]. Furthermore, hyperglycaemia induced microangiopathy leads to reversible metabolic, immunologic and ischemic injury of autonomic, motor and sensory nerves [12]. This causes a decrease in peripheral sensation and damages the nerve innervations of small muscles of the foot and fine vasomotor control of the pedal circulation [13].

When the nerve gets injured, the patient is at a higher risk of getting a minor injury without noticing it until it becomes an ulcer. The risk of developing foot ulcers in patients with sensory loss is increased up to seven-fold, compared to non-neuropathic patients with diabetes [4]. DM also affects the autonomic nervous system, leading to dryness and fissuring of skin, making it prone to infection. Autonomic system also controls the microcirculation of skin. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss [14,15]. Peripheral neuropathy has also been implicated in Charcot neuroarthropathy [16,17].

Vasculopathy

Hyperglycemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial cells synthesize nitric oxide which causes vasodilation and protects the blood vessels from endogenous injury. Hence, in hyperglycemia, there is perturbation of the physiological properties of nitric oxide which usually regulates the endothelial homeostasis, anticoagulation, leukocyte adhesion, smooth muscle cell proliferation and antioxidant capacity. Endothelium-derived

***Corresponding author:** Dr. Simerjit Singh, Department Of Orthopaedics, Melaka Manipal Medical College, Jalan Batu Hampar, Bukit Baru, Melaka, Malaysia, Tel: (606) 2925849/50/51; Fax: (606) 2817977; E-mail: Simer1980@Yahoo.Com

Received September 27, 2013; **Accepted** October 30, 2013; **Published** November 07, 2013

Citation: Singh S, Pai DR, Yuhhui C (2013) Diabetic Foot Ulcer – Diagnosis and Management. Clin Res Foot Ankle 1: 120. doi: 10.4172/2329-910X.1000120

vasodilators and nitric oxide are decreased hence leading to constriction of the blood vessels [18] and propensity for atherosclerosis [19], eventually leading to ischemia. Ischemia can also occur even in the presence of palpable pedal pulses [13]. The microcirculation is also disturbed due to arteriolar-venular shunting, reducing the blood circulation to the area of need [13]. Hyperglycemia in DM is also associated with increase in thromboxane A2 leading to plasma hypercoagulability [20]. Clinically the patient may have signs of vascular insufficiency such as claudication, night pain or rest pain, absent peripheral pulses, thinning of skin, loss of limb hair etc. [21].

Immunopathy

Compared to a healthy person's immune system, that of a patient with diabetes is much weaker. Thus, foot infection in a patient with diabetes is a limb threatening and debilitating condition. The hyperglycaemic state causes an elevation of pro-inflammatory cytokines and impairment of polymorphonuclear cell functions like chemotaxis, adherence, phagocytosis and intracellular killing [22]. Besides that, high blood glucose is a good medium for the growth of bacteria. The predominant organisms in diabetic foot infections are mainly aerobic gram positive cocci like *S. aureus* and *β*-hemolytic streptococci [23] but in one research conducted in India, gram-negative aerobes were the common microorganisms in diabetic foot [24]. The soft tissues of foot like plantar aponeurosis, tendons, muscles sheaths and fascia cannot resist infections. Furthermore, several compartments in the foot are interconnected and could not limit the spread of infection from one into another. This soft tissue infection can rapidly spread to the bones, causing osteitis. Thus a simple ulcer on the foot can easily result in complications such as osteitis/osteomyelitis and gangrene without appropriate care.

Mechanical stress

Insensate limbs are prone to injury which is often overlooked. The movements of the foot like flexion and extension are affected due to the damage to innervations of the foot muscles. Gradually, it leads to an alteration of the anatomical framework of the foot and formation of deformities. The deformities in turn create abnormal bony prominences and pressure points eventually predisposing to ulcers. Metatarsal fat pads are displaced distally, reducing the cushioning effects of the metatarsal heads and increase the pressure points which lead to callus formations that cause skin breakdown and ulceration [25,26]. Peripheral neuropathy promotes callus formation. The callus (callosity) contributes to high pressure areas and ulcer formation [27]. In the words of Duckworth et al. [28] "abnormally high pressures are more common in patients with diabetic neuropathy and almost all patients with a history of ulceration show high-pressure areas which correlate well with the site of previous ulceration." Usually, ulcers occur on the plantar aspect of great toe and heel.. However, ill-fitting shoes (which are the most common source of trauma) [29] can cause ulcers on the dorsal aspect [30]. Hence neuropathic foot ulcer formation in patients with diabetes has a complex multifactorial aetiopathogenesis wherein areas of high pressure complimented by peripheral neuropathy and associated skin changes lead to ulcer formation.

Grade 0	No ulcer in a high risk foot.
Grade 1	Superficial ulcer involving the full skin thickness but not underlying tissues.
Grade 2	Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
Grade 3	Deep ulcer with cellulitis or abscess formation, often with osteomyelitis.
Grade 4	Localized gangrene.
Grade 5	Extensive gangrene involving the whole foot.

Table 1: Wagner Classification of Diabetic Foot Ulcer [33].

Stage	Grade			
	0	I	II	III
A	pre- or post-ulcerative completely epithelized lesion	Superficial wound	Wound penetration upto tendon or capsule	Wound penetration upto bone 0r joint
B	Infection	Infection	Infection	Infection
C	Ischaemia	Ischaemia	Ischaemia	Ischaemia
D	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia	Infection and ischaemia

Table 2: The University of Texas wound classification system.

Neuroarthropathy

Charcot neuroarthropathy (CN) is a chronic painless progressive degenerative arthropathy resulting from the disturbance in sensory innervations of the affected joint. The impairment of the autonomic nervous system due to DM causes an increase in local blood supply and the resting blood flow is much higher than in the normal patient. The sudden increase in blood flow causes calcium to dissolve, leading to osteoclastic activity of the bone and thus damaging the bone [31]. Another theory is that the repetitive minor trauma to the insensate joints leads to fracture and disintegration [32]. The production of pro-inflammatory cytokines leads to uncontrolled osteolysis in CN. The cytokines such as tumor necrosis factor-α and interleukin-1β increase the expression of receptor activator of nuclear factor-κb (RANKL), which in turn causes maturation of osteoclasts by triggering production of nuclear factor-κb [32]. The hallmark deformity associated with this condition is midfoot collapse, also known as "rocker-bottom" foot. There might be hallux valgus deformity and loose bodies in the joint cavity. The deformities associated with CN also predispose for recurrent ulcerations.

Classification

To date, there are many classifications of Diabetic foot. However, the most commonly used classification systems are the Wagner-Ulcer Classification system [33] (Table1) and the University of Texas Wound Classification [34]. The University of Texas Wound Classification is a simple classification that considers grade (depth of the lesion) and stage (presence or absence of infection and ischaemia). The 'grade' ranges from 0 (pre- or post-ulcerative completely epithelized lesion) to III (involvement of bone or joint). 'Stage' ranges from A (absence of both infection and ischaemia), B (infection), C (ischaemia) and D (infection and ischaemia). The 'grade and stage' are combined to give the final classification (Table 2).

In both classifications, the higher the grade, the higher the risk of amputation with a longer healing time. Samson et al. found 'The University of Texas Wound classification system' to be better predictor of outcome [35]. However both the systems do not take into account the severity of infection [36]. Another validated classification system for DFUs that includes the severity of infection is The PEDIS (perfusion, extent, depth, infection, and sensation) system [36].

Diagnosis

History and physical examination

A proper investigation should be carried out in all patients with diabetes. A good history should include the duration of DM, neuropathic and peripheral vascular disease symptoms, previous ulcers or amputations and any other complication of DM like retinopathy or nephropathy [37]. A complete history will aid in assessing the severity

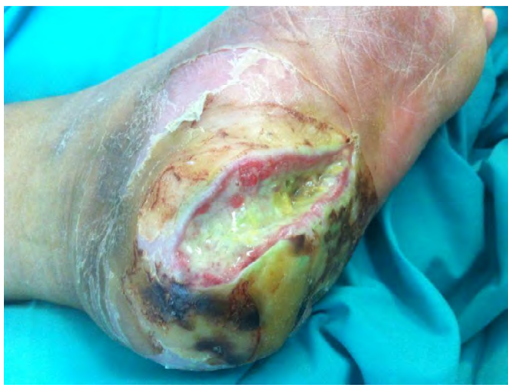

Figure 1: infected ulcer.

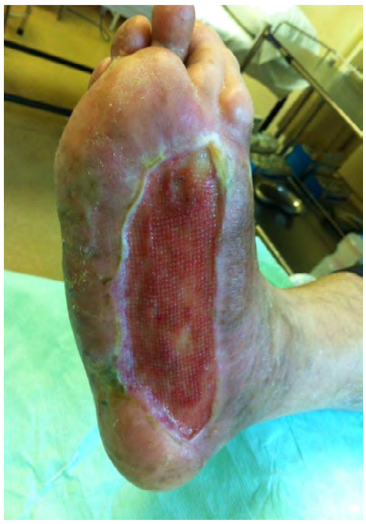

Figure 2: iSuperficial ulcer with healthy granulation tissue.

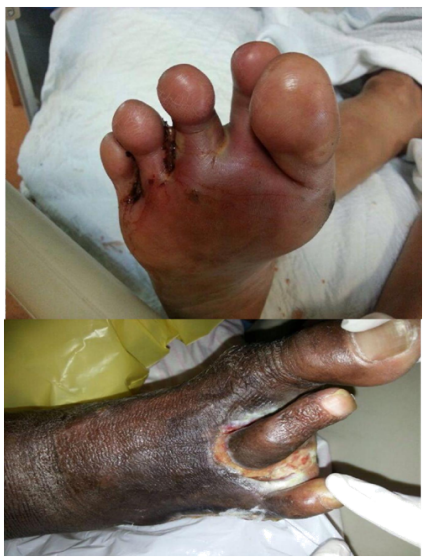

Figure 3: Infected ulcers: deeper infection is very likely with this appearance.

and risk of foot ulceration.

Foot examinations are reported to be effective in reducing the risk of amputations [38]. The foot should be carefully inspected for abnormalities like dry skin, fissures, deformities, and callosities. Ulcerations, prominent veins, and nail lesions should be looked out for. Changes in the foot temperature must be noted. An increase in temperature might suggest inflammation [39] while a decrease may indicate ischemia. Capillary refilling time should be assessed. All peripheral pulses must be examined. Pain, redness and swelling of the insensate foot/ankle should alert the examiner for CN, which can be easily confused with septic or gouty arthritis.

Examination of ulcer

A sterile stainless steel probe is used for assessing the ulcer to determine the depth and if there are sinus tracts present [40]. The location, size, shape, depth, base and margins of the ulcer should be examined clinically. Presence of granulation tissue or slough should be looked for in the floor of the ulcer to determine subsequent management (Figure1 and 2). Diagnosing a soft tissue infection in patient with diabetes is sometimes difficult, as the signs of inflammation of the overlying ulcer may be absent. The infection is mainly diagnosed based on presence of clinical signs and symptoms such as redness, warmth, tenderness, purulent secretions and fever [9] (Figure3). Palpation of the bone at the base of the ulcer with a sterile, blunt stainless steel probe has been suggested as positive predictor of underlying osteomyelitis [40].

Neurological testing

Sensory neuropathy can be tested by using monofilaments and biothesiometer. Semmes-Weinstein monofilaments are reported to be easy to use and help in predicting the risk of ulceration and amputation [41]. Caputo et al. [42] suggested annual testing of all patients with diabetes with a nylon monofilament to detect peripheral neuropathy. A 128 Hz tuning fork can also be used to test for vibratory sensation over the tip of the great toe bilaterally since metabolic neuropathies are more severe distally. Pain sensation should be tested as well. The Heart Rate Variability (HRV) with deep breathing or orthostatic blood pressure is measured to detect autonomic neuropathy [43] and any decrease or absence of HRV is considered the earliest sign of autonomic neuropathy in DM [44]. Specialised tests for sudomotor dysfunction include thermoregulatory sweat testing, quantitative sudomotor axon reflex testing, silicone impressions, the Sympathetic Skin Response (SSR), and the quantitative direct and indirect axon reflex testing [45]. These tests can be used in various combinations to localise the lesion of autonomic dysfunction (pre-ganglionic or post-ganglionic) [45].

Laboratory investigations

The standard procedure involves measuring blood glucose level and urine for glucose and ketones. Other investigations like full blood count, blood urea, electrolytes, and creatinine levels should be monitored regularly.. Glycosylated hemoglobin (HbA1C) is important to gauge the patient's overall glycemic control as HbA1c shows the mean blood sugar concentration best over previous weeks to months [46]. Hepatic and renal function tests are necessary for monitoring the patient's metabolic status. ESR can be done to assess the presence and response to treatment of infections like osteomyelitis [47]. Routine wound cultures are not recommended since all wounds harbour microorganisms [9]. However in the presence of invasive infection, cultures from the deeper tissue will help to identify the causative microorganisms.

Imaging

In case of diabetic foot, it is hard to assess the depth of the ulcer especially when there is pus and slough covering it. Also, it is hard to determine the extent of deep infection as the rubor of inflammatory response is minimal in subfascial sepsis [48]. X rays are helpful to determine the depth of foot ulceration and to assess presence of bone infection or neuroarthropathy. In CN, radiographs may reveal bony erosions, fractures, subluxation/dislocation of multiple joints, osteosclerotic features or united fractures [17]. Magnetic Resonance Imaging has emerged as a popular investigation for many of the foot problems. In Diabetic foot it is especially useful to detect infection and CN. It is used to evaluate the extent of foot infection by revealing the depth of ulceration, edema and localized fluid collections in the soft tissues, joints and tendon sheaths. Positron emission tomography demonstrates a high specificity for osteomyelitis [32].

Other investigations

Most of the DFUs may have silent osteomyelitis. Newman et al. found Indium-111 leukocyte scan to be 89% sensitive for diagnosing osteomyelitis in DFUs [49]. The treatment of ischaemic ulcers invariably requires surgical revascularization and hence differentiating them from neuropathic ulcers is paramount. Ankle brachial index (ABI) or toe-brachial index can be used to determine the extent of the vascular problem [50]. Values below 0.9 suggests an obstruction [51] while ABI less than 0.4 is associated with tissue necrosis and a significant risk for amputation [52]. Screening ABI every 5 years in patients with diabetes without any signs/symptoms of vascular insufficiency has been recommended. Pulse oximetry has also been reported to be as effective as ABI and the sensitivity of the test will be improved if used together with ABI [53]. The transcutaneous oxygen tension method is a reliable indicator of skin perfusion as periwound cutaneous perfusion is the critical physiological determinant of ulcer healing. TcPO2 less than 20mmHg has been associated with early wound healing failure [54]. Other investigations to detect vascular insufficiency include measuring absolute toe pressure, continuous-wave Doppler Ultrasonography, duplex ultrasonography, pulse volume recordings and angiography (CT, MRI or contrast). Pedobarography is a study of foot pressure and has been widely used in the research of diabetic foot [55]. In-shoe and barefoot peak plantar pressure measurement has also been suggested to assess foot at-risk and prevent ulcers [56].

In summary, DM affects multiple systems such as CVS, CNS, urinary, eye etc. Investigations in patients with DFU should be performed not only to assess local foot problems but also to assess the patient as a whole. Local investigations should be used to differentiate vascular from neurological problems, as the treatment of each is different. Detecting CN requires special investigations to differentiate it from other inflammatory conditions.

Management

Standard care for DFU is ideally provided by a multidisciplinary team by ensuring glycemic control, adequate perfusion, local wound care and regular debridement, off-loading of the foot, control of infection by appropriate antibiotics and management of comorbidities. Educating patients helps in preventing ulcers and their recurrence.

Debridement

Ulcers heal faster when the wound is clean as the devitalized necrotic tissues hinder cell migration and predispose it to infection and prohibit healing. Debridement of the wound may hasten healing by removing the dead necrotic tissue, particulate matter, or foreign materials, and reducing bacterial load [57]. The conventional way is to use a scalpel and excise all unwanted tissues including callus and eschar (sharp debridement). Since the necrotic tissue often extends beyond the ulcer bed, some authors recommend liberal debridement of deeper tissue beyond the ulcer boundary [58]. Using repeated 'piecemeal' debridements and herbal drinks, Wong et al. [59] reported 87% success rate in limb salvage. They stated that the radical debridement causes inadvertent damage to the vascularity of local tissue. Another approach is to completely excise the chronic ulcer and the underlying bony prominences and convert it to a fresh ulcer. Some authors have reported good results with this approach [60,61]. The limiting factors of sharp debridement include inadvertent bleeding, poor pain tolerance by the patient and lack of any objective markers to differentiate impaired and healthy tissue to ascertain the extent of debridement [57]. Other methods of wound debridement include physical debridement using wet-to-dry dressings; hydrodissection or hydrocision with the use of high pressure saline beam; enzymatic debridement using enzymes like collagenase and papain as ointment preparations; autolytic debridement with the use of moisture retaining dressings; and biological debridement with use of larvae of common green bottle fly (*Lucilia sericata*). Maggot therapy is recommended for DFUs when surgical debridement and antibiotics fail to improve tissue healing [62]. Occasionally sharp debridement is combined with other forms of debridement to achieve ulcer healing.

Dressings

Dressing materials used include saline-moistened gauze dressings (wet-to-dry); moisture retaining dressings (hydrogels, hydrocolloids, hydrofibres, transparent films and alginates) that provide physical and autolytic debridement respectively; and antiseptic dressings (silver dressings, cadexomer). New advanced dressings are being researched, for example Vulnamin© gel made of amino acids and hyaluronic acid are used along with elastocompression has shown favourable results [63]. Promogran© by Johnson and Johnson's is a freeze dried matrix composed of collagen and oxidized regenerated cellulose [64]. When in contact with wound exudates, it forms a biodegradable gel that physically binds and inactivates matrix metalloproteases that affects wound healing. A randomized control trial found it to be efficacious especially for ulcers of less than six months duration [65]. Medicated honey has anti-inflammatory, antiseptic and osmotic properties and has been used as such or in combination with sterile dressings [66].

Offloading

Total contact cast (TCC), removable cast walkers, custom shoes, half-shoes, soft heel shoes, padded socks, and shoe inserts, wheelchairs, crutches etc. have been used for offloading the foot to prevent and treat the DFUs. The aim is to reduce the plantar pressure by redistributing it to a larger area, to avoid shear and friction, and to accommodate the deformities. A randomized control trial compared the efficacy of a TCC, removable cast walker and half-shoe in patients with DFUs found TCC to be the most effective modality [67]. TCC was also found to be superior to traditional dressings in treatment of plantar DFUs [68]. However, the limiting factors for TCC include requirement of trained personnel for its application and high costs due to need for frequent cast changings. Removable cast walkers such as Aircast walkers allow for surveillance of skin and dressing changes. One study [69] found them to be more cost effective than TCC. A recent systematic review found non-removable off-loading devices (for example TCC) to be more effective for ulcer healing than removable off-loading devices (for example, removable cast walker) [70].

Medical treatment

Strict glycaemic control should be maintained with the use of diabetic diet, oral hypoglycaemic agents and insulin. Infections of the soft tissue and bone are the leading cause of hospital admissions in patients with DFUs [71]. As stated earlier, the diagnosis of infection in DFUs is primarily clinical. Culture from the deeper tissues aids in selecting appropriate antibiotics. While awaiting the results of wound culture, patients can be given empirical broad spectrum antibiotic regimen. Antibiotics are preferably given intravenously for limb threatening infections.

Gabapentin and pregabalin have been used for symptomatic relief for painful neuropathy in DM [72]. A recent study in Greece found pregabalin to be more cost effective as compared to gabapentin [73]. A double blinded randomised trial study of tramadol has been proven to be successful in alleviating pain symptoms in diabetic neuropathy [74]. Aldose reductase inhibitors are being studied and have shown to be effective in inhibiting progression of peripheral neuropathy [75,76]. Autonomic dysfunction may require the use of beta-blockers [14]. Medical management of symptoms of vascular insufficiency like intermittent claudication includes Cilostazol or Pentoxifylline besides exercise therapy.

Adjuvant therapy

Management strategies that target the defective extracellular matrix (ECM) in DFUs include the skin substitutes that are derived from growing skin cells of autologous or allogenic source onto collagen or polylactic acid [77]. They contain matrix which can be cellular for example DermagraftW (Shire Regenerative Medicine, Inc. La Jolla, California, United States) and Apligraf® (Novartis Pharma AG, Basel, Switzerland) or acellular like OasisW (Healthpoint, Ltd Fort Worth, Texas, United States) and Matriderm® (MedSkin Solutions Dr Suwelack AG, Germany) [78-80]. They promote wound healing by "promoting revascularization, cellular migration, and repopulation of wound fields through provision of an appropriate scaffold material to facilitate these processes" [81]. They should not be used as replacement to skin grafting or flap coverage as stressed by Brem et al. [82]. The high cost, limited availability, risk of transmissible diseases and immunological rejection limit their widespread use [77].

Hyperbaric Oxygen (HBO) has been found to be a useful adjunctive therapy for DFUs and is associated with decrease in amputation rates [83,84]. The beneficial role of topical oxygen therapy in treating chronic wounds has also been documented [85,86]. Negative pressure wound therapy involves creating a sub-atmospheric pressure at the wound site and draining out the exudates. It improves oxygenation, cellular proliferation and wound granulation and reduces bacterial load and inhibitory cytokines [87]. A study found better efficacy and decreased amputation rate with the use of negative pressure wound therapy compared to moist dressings (hydrogels, alginates) in the management of DFUs [88]. Extracorporeal shock wave therapy acts by increasing angiogenesis and blood supply, cellular proliferation and thus hastening wound healing. Some studies have found improved results with the use of shock therapy in DFUs [89,90]. Low energy lasers have also been used as an adjunctive therapy for DFUs [91,92]. They act by increasing microcirculation and improving healing of the ischaemic DFU. Growth factors for example recombinant human platelet derived growth factor (rhPDGF) [93], topical platelets [94] and platelet rich plasma [95] have also been used in treating DFUs and have shown favourable results.

Surgical management

Wound closure: Wound closure is attempted once the ulcer is clean with healthy granulation tissue. Primary closure is possible for small wounds; tissue loss can be covered with the help of skin graft, flap or commercially available skin substitutes. Split-thickness skin grafts are preferred over full thickness grafts. In one study [96], topical phenytoin application before autografting promoted granulation tissue formation and was found to enhance graft uptake in large DFUs. Yamaguchi et al. [97] used a combined method of treating DFUs by scraping the exposed bone till it bled and covered it with epidermal sheets obtained from suction blisters of patients. The authors stated 100% success rate with this technique. Another study [98] comparing skin grafting and standard dressing in the management of DFUs found better results in skin graft group in terms of decreased healing time and length of hospital stay. DFUs with exposed tendon, ligament or bone require coverage with muscle flaps [99]. Flaps can be either local (for smaller wounds) or free-flaps (for large area). Latissimus dorsi, gracilis or rectus abdominis are the commonly used free flaps [100]. The limitations of standard flaps include donor site morbidity, difficulty in shaping the flaps and interference with footwear [100].

Revascularization surgery: Patients with peripheral ischemia who have significant functional disability should undergo surgical revascularization if medical management fails. This may decrease the amputation risk in patients with ischaemic DFUs [101]. Brem et al. [102] advocated early revascularization after controlling the infection in cases of ischaemic DFUs. The procedures include open (bypass grafting or endarterectomy) or endovascular techniques (angioplasty with or without stent) [103].

The traditional method of treatment for ischemic limbs is surgical bypass. Autologous vein (preferably) or synthetic grafts may be used. Peroneal and dorsalis pedis bypass have been used and have acceptable limb salvage rates [104]. With regard to angioplasty, good results in terms of low post procedure amputation rate (5.2%) have been reported with the use of percutaneous transluminal angioplasty of infrapopliteal artery [105]. However a Cochrane review by Berridge et al. found no difference in limb salvage or death at one year between initial surgery and initial thrombolysis [106]. The authors concluded that the higher risk of complications associated with thrombolysis must be balanced against risks of surgery in every case.

Amputation: Amputations are generally used as a treatment of last resort when other measures fail. However, they may be also performed earlier to allow for earlier return to work or better functional status. For example, amputation is preferred over prolonged antibiotic therapy in case of toe infections (except for the great toe) [107]. Patients with DM account for around 40-60% of all the lower extremity amputations and most of them result from deterioration of foot ulcer [108]. Schaper et al. [36] mentioned that patients with diabetes who have a foot infection are around 50 times more likely to be hospitalized and 150 times more likely to undergo lower extremity amputation than those without foot infections. Determining the level of amputation requires the trade-offs between vascularity and limb length. As a general principle, it is imperative to save as much limb length as possible. Clinical examination, ABI and transcutaneous oxygen measurements (before and after inhalation of oxygen) can be used to decide the level of amputation, but of these transcutaneous oxygen measurements are preferred [109]. The commonly performed amputations for ischaemic DFUs include toe, Ray, transmetatarsal, tarsometatarsal (Lisfranc), midtarsal (Chopart), hindfoot and ankle (Pirogoff, Boyd, Syme's) and trans-tibial. A two-stage technique of Syme's amputation has been described to decrease the risk of infection and wound healing reported with it in patients with diabetes [110]. However Pinzur et al. in a randomized control trial found single-stage Syme's amputation as effective as two-stage amputation [111].

Tenectomy of the Achilles tendon is preferred along with Lisfranc and Chopart amputations to avoid equinus deformity. Tourniquet, thin skin flaps and suturing of muscles to bones (myodesis) are avoided [109]. Avoiding hematoma formation by meticulous haemostasis is desired. Post-amputation, simple moistened gauze dressings are preferred. Depression and anxiety are the common psychiatric illness in amputees [112,113] and the decision to amputate a patient's limb must be made in consultation with the patient and with comprehensive counselling. Exostectomies, arthrodesis and amputation are done to manage complications such as CN. The indications for surgery in CN are failed conservative management with deformity, joint instability, infection and recurrent ulceration [32]. Osteomyelitis usually responds to antibiotics without the need for surgery. However, if required the infected bone can be resected if it does not affect the architecture of the foot [114].

Prevention

Patient education and self-care practices like maintaining foot hygiene and nail care should be promoted. Skin is kept moisturized with the application of topical moisturizers after washing the feet gently with soap and water [21]. Harsher measures like hot soaks, heating pads and topical agents such as hydrogen peroxide, iodine and astringents are better avoided [21]. There is direct correlation between glycemic control and ulcer formation [115]. Neuropathic feet are warmer and temperature differences of 2-7°C have been noted between neuropathic and non-neuropathic feet [116]. Hence self-monitoring may reduce the risk of ulceration [39]. Smoking and alcohol consumption should be minimized, though the direct link between them and DFUs is weak [115,116]. Offloading and appropriate footwear to relieve focal high pressure areas is recommended for foot at-risk. Other comorbidities like hypertension and hyperlipidaemia which predispose to vascular occlusion should be treated. Prevention of ulcer recurrence may also require corrective surgical interventions.

Factors Affecting Healing

Picwell et al. [117] studied factors affecting healing of diabetic foot ulcers that included the location of ulcer, duration of diabetes, ulcer duration, the presence of heart failure and peripheral arterial disease. The proximal location of the ulcer corresponded with maximal healing time with no difference in healing times between plantar and nonplantar ulcers. Sheehan et al. [118] noted that the percentage change in foot ulcer area after 4 weeks can predict of healing at the end of 12 weeks and can be used as an early indicator of unresponsiveness to treatment. Increased size and depth of ulcer have been associated with poor healing [119].

Summary

Diabetic foot is a chronic complication of DM which is not accorded the "glamour" status of its more illustrious sisters like coronary heart disease, cerebrovascular disease, nephropathy or retinopathy. Nonetheless it is responsible for a significant proportion of morbidity in DM, causing severe patient distress and frequently permanent disability. It is therefore necessary to pay special attention to this complication when reviewing, or counselling, patients with DM. This is all the more so as it is a complication that is preventable by simple measures that can largely be taken by the patient himself. Frequent clinical examination of the feet and related systems forms the mainstay of detecting diabetic foot; investigations are only an adjunct to clinical examination. The treatment is usually conservative and a limb sparing approach is used, along with proper diabetic control. Management of aetiological factors like vasculopathy, neuropathy and infection is essential to get good outcomes. Amputation is usually used as a last resort in non-salvageable limbs. Above all, this is one condition which proves the maxim that "prevention is better than cure".

References

1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, et al. (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2•7 million participants. Lancet 378: 31-40.
2. http://www.who.int/mediacentre/factsheets/fs138/en/.
3. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010) Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation 121: 1356-1364.
4. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053.
5. Pendsey SP (2010) Understanding diabetic foot. Int J Diabetes Dev Ctries 30: 75-79.
6. Boulton AJ (2004) The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia 47: 1343-1353.
7. Carrington AL, Mawdsley SK, Morley M, Kincey J, Boulton AJ (1996) Psychological status of diabetic people with or without lower limb disability. Diabetes Res Clin Pract 32: 19-25.
8. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R (2008) Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil 89: 422-429.
9. Boulton AJ, Kirsner RS, Vileikyte L (2004) Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med 351: 48-55.
10. Brem H, Tomic-Canic M (2007) Cellular and molecular basis of wound healing in diabetes. J Clin Invest 117: 1219-1222.
11. Clayton W, Elcasy TA (2009) A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients. Clin Diabetes 27: 52-58.
12. Younger DS, Rosoklija G, Hays AP (1998) Diabetic peripheral neuropathy. Semin Neurol 18: 95-104.
13. Jeffcoate WJ, Harding KG (2003) Diabetic foot ulcers. Lancet 361: 1545-1551.
14. Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. Diabetes Care 26: 1553-1579.
15. Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, et al. (1999) A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care 22: 1036-1042.
16. Perrin BM, Gardner MJ, Suhaimi A, Murphy D (2010) Charcot osteoarthropathy of the foot. Aust Fam Physician 39: 117-119.
17. Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S (2002) Charcot neuroarthropathy in diabetes mellitus. Diabetologia 45: 1085-1096.
18. Creager MA, Lüscher TF, Cosentino F, Beckman JA (2003) Diabetes and vascular disease, pathophysiology,clinical consequences, and medical therapy: Part I. Circulation. 108: 1527-1532.
19. Dokken BB (2008) The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids. Diabetes Spectr 21: 160-165.
20. Paraskevas KI, Baker DM, Pompella A, Mikhailidis DP (2008) Does diabetes mellitus play a role in restenosis and patency rates following lower extremity peripheral arterial revascularization? A critical overview. Ann Vasc Surg 22: 481-491.
21. Armstrong DA, Lavery LA (1998) Diabetic foot ulcers: prevention, diagnosis and classification. AmFamphysician57: 1325-1332.
22. Gupta S, Koirala J, Khardori R, Khardori N (2007) Infections in Diabetes Mellitus and Hyperglycemia. Infect Dis Clin North Am 21: 617-638.
23. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, et al. (2004) Diagnosis and Treatment of Diabetic Foot Infections. Clin Infect Dis 39: 885-910.
24. Gadepalli R, Dhawan B, Sreenivas V, Kapil A, Ammini AC, et al. (2006) A clinico-microbiological study of diabetic foot ulcers in an Indian tertiary care hospital. Diabetes Care 29: 1727-1732.

25. Bowering CK (2001) Diabetic foot ulcers. Pathophysiology, assessment, and therapy. Can Fam Physician 47: 1007-1016.

26. Murray HJ, Young MJ, Hollis S, Boulton AJ (1996) The association between callus formation, high pressures and neuropathy in diabetic foot ulceration. Diabet Med 13: 979-982.

27. Rosen RC, Davids MS, Bohanske LM, Lemont H (1985) Hemorrhage into plantar callus and diabetes mellitus. Cutis 35: 339-341.

28. Duckworth T, Boulton AJ, Betts RP, Franks CI, Ward JD (1985) Plantar pressure measurements and the prevention of ulceration in the diabetic foot. J Bone Joint Surg Br 67: 79-85.

29. Macfarlane RM, Jeffcoate WJ (1997) Factors contributing to the presentation of diabetic foot ulcers. Diabet Med 14: 867-870.

30. Peters EJ, Armstrong DA, Lavery LA (2007) Risk Factors for Recurrent Diabetic Foot Ulcers:sitematters. Diabetes Care 30: 2077-2079.

31. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJM, Edmonds M, et al. (2011) The Charcot Foot in Diabetes. Diabetes 34: 2123-2129.

32. Madan SS, Pai DR (2013) Charcot neuroarthropathy of the foot and ankle. Orthop Surg 5: 86-93.

33. Wagner FW Jr (1981) The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 2: 64-122.

34. Lavery LA, Armstrong DG, Harkless LB (1996) Classification of diabetic foot wounds. J Foot Ankle Surg 35: 528-531.

35. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, et al. (2001) A Comparison of Two Diabetic Foot Ulcer Classification Systems. The Wagner and the University of Texas wound classification systems. Diabetes Care 24: 84-88.

36. Schaper NC, Dryden M, Kujath P, Nathwani D, Arvis P, et al. (2013) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the relief study. Infection 41: 175-186.

37. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG (1998) Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 158: 157-162.

38. Mayfield JA, Reiber GE, Nelson RG, Greene T (2000) Do foot examinations reduce the risk of diabetic amputation? J Fam Pract 49: 499-504.

39. Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, et al. (2007) Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. Am J Med 120: 1042-1046.

40. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW (1995) Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 273: 721-723.

41. Mayfield JA, Sugarman JR (2000) The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. J Fam Pract 49: S17-29.

42. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW (1994) Assessment and management of foot disease in patients with diabetes. N Engl J Med 331: 854-860.

43. Rogers LC, Bevilacqua NJ (2008) The diagnosis of Charcot foot. Clin Podiatr Med Surg 25: 43-51, vi.

44. Unger J, Cole BE (2007) Recognition and management of diabetic neuropathy. Prim Care 34: 887-913, viii.

45. Illigens BM, Gibbons CH (2009) Sweat testing to evaluate autonomic function. Clin Auton Res 19: 79-87.

46. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, et al. (1976) Correlation of Glucose Regulation and Hemoglobin AIc in Diabetes Mellitus. N Engl J Med 295: 417-420.

47. Rabjohn L, Roberts K, Troiano M, Schoenhaus H (2007) Diagnostic and prognostic value of erythrocyte sedimentation rate in contiguous osteomyelitis of the foot and ankle. J Foot Ankle Surg 46: 230-237.

48. Naraynsingh V, Maharaj R, Dan D, Hariharan S (2011) Puncture wounds in the diabetic foot: importance of X-ray in diagnosis. Int J Low Extrem Wounds 10: 98-100.

49. Newman LG, Waller J, Palestro CJ, Schwartz M, Klein MJ, et al. (1991) Unsuspected osteomyelitis in diabetic foot ulcers: diagnosing and monitoring by leukocyte scanning with indium In111 oxyquinolone. JAMA 266: 1246-1251.

50. Shin JB, Seong YJ, Lee HJ, Kim SJ, Park JR (2000) Foot screening technique in a Diabetic population. J Korean Med Sci 15: 78-82.

51. Doobay AV, Anand SS (2005) Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 25: 1463-1469.

52. Reiber GE, Pecoraro RE, Koepsell TD (1992) Risk factors for amputation in patients with diabetes mellitus. A case-control study. Ann Intern Med 117: 97-105.

53. Parameswaran GI, Brand K, Dolan J (2005) Pulse oximetry as a potential screening tool for lower extremity arterial disease in asymptomatic patients with diabetes mellitus. Arch Intern Med 165: 442-446.

54. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL (1991) Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. Diabetes 40: 1305-1313.

55. Lobmann R, Kayser R, Kasten G, Kasten U, Kluge K, et al. (2001) Effects of preventative footwear on foot pressure as determined by pedobarography in diabetic patients: a prospective study. Diabet Med 18: 314-319.

56. Patry J, Belley R, Côté M, Chateau-Degat ML (2013) Plantar pressures, plantar forces, and their influence on the pathogenesis of diabetic foot ulcers: a review. J Am Podiatr Med Assoc 103: 322-332.

57. Pai, DR, Madan SS (2013) Techniques in Chronic Wound Management: Review of the Literature and Recent Concepts. J Nov Physiother 3: 2.

58. Shi JY, Zhou SL (1996) Diabetic teno-necrosis—a clinical study [in Chinese]. Shanghai J Trad Chin Med 5: 27-31.

59. Wong MW, Leung PC, Wong WC (2001) Limb salvage in extensive diabetic foot ulceration-a preliminary clinical study using simple debridement and herbal drinks. Hong Kong Med J 7: 403-407.

60. Piaggesi A, Schipani E, Campi F, Romanelli M, Baccetti F, et al. (1998) Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. Diabet Med 15: 412-417.

61. Armstrong DG, Lavery LA, Vazquez JR, Short B, Kimbriel HR, et al. (2003) Clinical efficacy of the first metatarsophalangeal joint arthroplasty as a curative procedure for hallux interphalangeal joint wounds in patients with diabetes. Diabetes Care 26: 3284-3287.

62. Mumcuoglu KY, Ingber A, Gilead L, Stessman J, Friedmann R, et al. (1998) Maggot therapy for the treatment of diabetic foot ulcers. Diabetes Care 21: 2030-2031.

63. Abbruzzese L, Rizzo L, Fanelli G, Tedeschi A, Scatena A, et al. (2009) Effectiveness and safety of a novel gel dressing in the management of neuropathic leg ulcers in diabetic patients: a prospective double-blind randomized trial. Int J Low Extrem Wounds 8: 134-140.

64. http://www.dressings.org/Dressings/promogran.html.

65. Veves A, Sheehan P, Pham HT (2002) A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs. standard treatment in the management of diabetic foot ulcers. Arch Surg 137: 822-827.

66. Shukrimi A, Sulaiman AR, Halim AY, Azril A (2008) A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. Med J Malaysia 63: 44-46.

67. Armstrong DG, Nguyen HC, Lavery LA, Van Schie CH, Boulton AJ, et al. (2001) Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care 24: 1019-1022.

68. Mueller MJ, Diamond JE, Sinacore DR, Delitto A, Blair VP 3rd, et al. (1989) Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care 12: 384-388.

69. Verity S, Sochocki M, Embil JM, Trepman E (2008) Treatment of Charcot foot and ankle with a prefabricated removable walker brace and custom insole. Foot Ankle Surg 14: 26-31.

70. Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL (2013) Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev 29: 183-193.

71. Gibbons GW (1987) The diabetic foot: amputations and drainage of infection. J Vasc Surg 5: 791-793.

72. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, et al. (1998) Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 280: 1831-1836.

73. Athanasakis K, Petrakis I, Karampli E, Vitsou E, Lyras L, et al. (2013) Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: a cost effectiveness analysis for the Greek healthcare setting. BMC Neurol 13: 56.

74. Harati Y, Gooch C, Swenson M, Edelman S, Greene D, et al. (1998) Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 50: 1842-1846.

75. Hotta N, Kawamori R, Fukuda M, Shigeta Y; Aldose Reductase Inhibitor-Diabetes Complications Trial Study Group (2012) Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on progression of diabetic neuropathy and other microvascular complications: multivariate epidemiological analysis based on patient background factors and severity of diabetic neuropathy. Diabet Med 29: 1529-1533.

76. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, et al. (2006) Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. Diabetes Care 29: 1538-1544.

77. Rizzi SC, Upton Z, Bott K, Dargaville TR (2010) Recent advances in dermal wound healing: biomedical device approaches. Expert Rev Med Devices 7: 143-154.

78. Lev-Tov H, Li CS, Dahle S, Isseroff RR (2013) Cellular versus acellular matrix devices in treatment of diabetic foot ulcers: study protocol for a comparative efficacy randomized controlled trial. Trials 14: 8.

79. Redekop WK, McDonnell J, Verboom P, Lovas K, Kalo Z (2003) The cost effectiveness of Apligraf® treatment of diabetic foot ulcers. Pharmacoeconomics 21: 1171-1183.

80. Jeon H, Kim J, Yeo H, Jeong H, Son D, et al. (2013) Treatment of diabetic foot ulcer using matriderm in comparison with a skin graft. Arch Plast Surg 40: 403-408.

81. Greaves NS, Iqbal SA, Baguneid M, Bayat A (2013) The role of skin substitutes in the management of chronic cutaneous wounds. Wound Repair Regen 21: 194-210.

82. Brem H, Young J, Tomic-Canic M, Isaacs C, Ehrlich HP (2003) Clinical efficacy and mechanism of bilayered living human skin equivalent (HSE) in treatment of diabetic foot ulcers. Surg Technol Int 11: 23-31.

83. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, et al. (1996) Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes Care 19: 1338-1343.

84. Liu R, Li L, Yang M, Boden G, Yang G (2013) Systematic review of the effectiveness of hyperbaric oxygenation therapy in the management of chronic diabetic foot ulcers. Mayo Clin Proc 88: 166-175.

85. Kalliainen LK, Gordillo GM, Schlanger R, Sen CK (2003) Topical oxygen as an adjunct to wound healing: a clinical case series. Pathophysiology 9: 81-87.

86. Sen CK, Khanna S, Gordillo G, Bagchi D, Bagchi M, et al. (2002) Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. Ann N Y Acad Sci 957: 239-249.

87. Plikaitis CM, Molnar JA (2006) Subatmospheric pressure wound therapy and the vacuum-assisted closure device: basic science and current clinical successes. Expert Rev Med Devices 3: 175-184.

88. Blume PA, Walters J, Payne W, Ayala J, Lantis J (2008) Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of Diabetic Foot Ulcers A multicenter randomized controlled trial. Diabetes care 31: 631-636.

89. Wang CJ, Wu RW, Yang YJ (2011) Treatment of diabetic foot ulcers: a comparative study of extracorporeal shockwave therapy and hyperbaric oxygen therapy. Diabetes Res Clin Pract 92: 187-193.

90. Moretti B, Notarnicola A, Maggio G, Moretti L, Pascone M, et al. (2009) The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC Musculoskelet Disord 10: 54.

91. Schindl A, Schindl M, Schön H, Knobler R, Havelec L, et al. (1998) Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. Diabetes Care 21: 580-584.

92. Landau Z, Schattner A (2001) Topical hyperbaric oxygen and low energy laser therapy for chronic diabetic foot ulcers resistant to conventional treatment. Yale J Biol Med 74: 95-100.

93. Hollinger JO, Hart CE, Hirsch SN, Lynch S, Friedlaender GE (2008) Recombinant human platelet-derived growth factor: biology and clinical applications. J Bone Joint Surg Am 90: 48-54.

94. Scherer SS, Tobalem M, Vigato E, Heit Y, Modarressi A, et al. (2012) Nonactivated versus thrombin-activated platelets on wound healing and fibroblast-to-myofibroblast differentiation in vivo and in vitro. Plast Reconstr Surg 129: 46-54.

95. Villela DL, Santos VL (2010) Evidence on the use of platelet-rich plasma for diabetic ulcer: a systematic review. Growth Factors 28: 111-116.

96. Younes N, Albsoul A, Badran D, Obedi S (2006) Wound bed preparation with 10-percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. Dermatol Online J 12: 5.

97. Yamaguchi Y, Yoshida S, Sumikawa Y, Kubo T, Hosokawa K, et al. (2004) Rapid healing of intractable diabetic foot ulcers with exposed bones following a novel therapy of exposing bone marrow cells and then grafting epidermal sheets. Br J Dermatol 151: 1019-1028.

98. Mahmoud SM, Mohamed AA, Mahdi SE, Ahmed ME (2008) Split-skin graft in the management of diabetic foot ulcers. J Wound Care 17: 303-306.

99. Attinger CE, Ducic I, Cooper P, Zelen CM (2002) The role of intrinsic muscle flaps of the foot for bone coverage in foot and ankle defects in diabetic and nondiabetic patients. Plast Reconstr Surg 110: 1047-1054.

100. Schirmer S, Ritter RG, Fansa H (2013) Vascular surgery, microsurgery and supramicrosurgery for treatment of chronic diabetic foot ulcers to prevent amputations. PLoS One 8: e74704.

101. LoGerfo FW, Gibbons GW, Pomposelli FB Jr, Campbell DR, Miller A, et al. (1992) Trends in the care of the diabetic foot. Expanded role of arterial reconstruction. Arch Surg 127: 617-620.

102. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ (2006) Evidence-based protocol for diabetic foot ulcers. Plast Reconstr Surg 117: 193-209.

103. Albayati MA, Shearman CP (2013) Peripheral Arterial Disease and Bypass Surgery in the Diabetic Lower Limb. Med Clin North Am 97: 821-834.

104. DarlingRC 3rd, Chang BB, Shah DM, Leather RP (1997) Choice of peroneal or dorsalis pedis artery bypass for limb salvage. Semin Vasc Surg 10: 17-22.

105. Faglia E, Mantero M, Caminiti M, Caravaggi C, De Giglio R, et al. (2002) Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med 252: 225-232.

106. Berridge DC, Kessel DO, Robertson I (2013) Surgery versus thrombolysis for initial management of acute limb ischaemia. Cochrane Database Syst Rev 6:CD002784.

107. Benton GS, Kerstein MD (1985) Cost effectiveness of early digit amputation in the inpatient with diabetes. Surg Gynecol Obstet 161: 523-524.

108. Apelqvist J, Larsson J (2000) What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev 16: 75-83.

109. Canale ST, Beaty JH (2008) Surgical principles of amputations: Campbell's operative orthopaedics. (11thedn.) Mosby Elssevier, Philadelphia, Pennsylvania, USA.

110. Pinzur MS, Morrison C, Sage R, Stuck R, Osterman H, et al. (1991) Syme's two-stage amputation in insulin-requiring diabetics with gangrene of the forefoot. Foot Ankle 11: 394-396.

111. Pinzur MS, Smith D, Osterman H (1995) Syme ankle disarticulation in peripheral vascular disease and diabetic foot infection: the one-stage versus two-stage procedure. Foot Ankle Int 16: 124-127.

112. Atherton R, Robertson N (2006) Psychological adjustment to lower limb amputation amongst prosthesis users. Disabil Rehabil 28: 1201-1209.

113. 113. Singh R, Ripley D, Pentland B, Todd I, Hunter J, et al. (2009). Depression and anxiety symptoms after lower limb amputation: the rise and fall. Clin Rehabil 23: 281-286.

114. Lipsky BA (1997) Osteomyelitis of the foot in diabetic patients. Clin Infect Dis 25: 1318-1326.

115. 115.Moss SE, Klein R, Klein BE (1992) The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med 152: 610-616.

116. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM (1998) Preventive foot care in people with diabetes. Diabetes care 21: 2161-2177.

117. Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC, et al. (2013) Diabetic foot disease: impact of ulcer location on ulcer healing. Diabetes Metab Res Rev 29: 377-383.

118. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A (2003) Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes care 26: 1879-1882.

119. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA (2000) Risk factors for delayed healing of neuropathic diabetic foot ulcers: a pooled analysis. Arch Dermatol 136: 1531-1535.